The stereochemistry and medicinal chemistry of 3-substituted 6,7-benzomorphans.

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THE STEREOCHEMISTRY AND MEDICINAL CHEMISTRY OF 3-SUBSTITUTED 6,7-BENZOMORPHANS

THESIS

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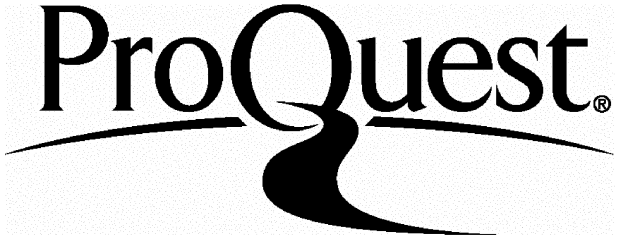
This research has been carried out in the School of Pharmacy and Pharmacology of the University of Bath, under the supervision of Prof. R.T. Parfitt, B. Pharm., Ph.D., F.P.S., C. Chem., F.R.S.C.



TO THE MEMORY OF MY MOTHER

MRS. S.T. OGUNDAINI

who saw the beginning of this work but

could not see the end.

ACKNOWLEDGEMENTS

I wish to express my sincere gratitude to Prof. R.T. Parfitt for his wonderful supervision and encouragement in the course of this work.

I would also like to express my thanks to the following: Drs. A.F. Casy and G. H. Dewar for their helpful discussion and readiness to help at all times; the School of Pharmacy, Brunswick Square, for the micro-analyses of the compounds reported in the thesis; Dr. A.E. Jacobson of the National Institute of Health, Bethseda, for the mouse hot plate tests; Messrs R. Hartell, D. Wood and K. Smith for skilled technical assistance and to all my friends and colleagues who have all been helpful in more than one way.

I thank Mrs Judy Harbutt for typing this thesis and Eve Gonty for all her troubles.

Finally, I wish to express my sincere gratitude to the Association of Commonwealth Universities for providing me with the Scholarship to pursue this work.

SUMMARY

A brief survey of synthetic narcotic analgesics and newer developments in analgesic research is given. In particular, the chemistry and structure-biological-activity relationships in the 6,7-benzomorphan area is reviewed. The higher agonist potency of 4,5-dimethyl-6,7-benzomorphan over the *cis*-3,5-dimethyl isomer has been attributed tentatively to steric hindrance of the nitrogen lone electron pair in the latter by an equatorial 3-methyl group. A more detailed investigation of this claim is therefore the subject of the present work.

A series of 3-monosubstituted and 3,3-disubstituted-6,7-benzomorphans have been synthesized and characterised. The configuration of each is established by ^{1}H and ^{13}C n.m.r. spectroscopy. The differences in analgesic activity is explained by substituent participation in receptor interactions rather than by hindrance of nitrogen non bonding electrons, and this is considered in some detail.

2'-Hydroxyl analogues of 2-alkyl-*cis*-3,5-dimethyl-6,7-benzomorphan and the corresponding 2,4,5-trimethyl isomer have been prepared and evaluated to complement the data on the 5,9-dimethyl isomers. The inactivity of 2'-hydroxyl-2,4,5-trimethyl-6,7-benzomorphan relative to the non-phenolic analogue has highlighted the need for further investigation in this area since, in general, the observation is that 2'-hydroxyl group leads to enhancement of activity in 6,7-benzomorphans. Some suggestions for additional

work are also made.

Lastly, some potential analgesics in the 6,7-benzomorphan series having novel 2-amidino substituents have been prepared and at present are being evaluated.

CONTENTS

PART I

INTRODUCTION

CHAPTER 1

Historical Review and Recent Developments in Analgesic Research

1.1 Early History

Pain is a subjective experience that is interpreted as a symptomatic evidence of impending or actual tissue damage. The treatment of pain over the years has greatly been influenced by man's understanding of the subject. Some of the early methods used include herbal remedies, prayer and supplication, acupuncture, hypnosis, electrical stimulation and, later, analgesics.

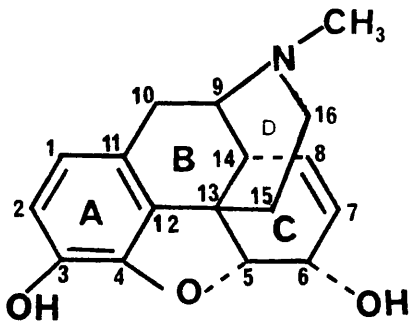
However, no other pain reliever has stood the test of time in a manner comparable to opium - the dried exudate from the unripe seed capsules of the opium poppy *Papaver somniferum*. The first reference to opium was by the Sumerians around 4000 B.C., when it was known as 'hul gil' or joy plant. The ancient Greeks and Romans used opium as a soporific and pain killer, and in Europe in the early 19th century opium preparations, such as the pill, and laudanum were widely used. Due to unreliability of these preparations a young German chemist Sertuner[1] in 1805, isolated the active ingredient, the alkaloid morphine (1.*1*) from opium. By the mid 19th century, the use of pure morphine rather than the crude opium preparations had spread. Unfortunately, in addition to its analgesic action, morphine has other central effects: it causes the constriction of the pupils, changes in mood and perception, and depression of the respiratory centre. Furthermore, prolonged usage leads to tolerance and physical dependence (addiction).

The recognition of this problem of addiction led to numerous efforts directed towards understanding the basic mechanisms of action

of the drug, and stimulated the continuing search for effective drug alternatives lacking the side effects characteristic of morphine.

1.2 Synthetic Analgesics

The determination of the total structure of morphine (1.*1*) by Gulland and Robinson[2] in 1925 was a milestone in the search for better analgesics. It encouraged chemical modifications of this



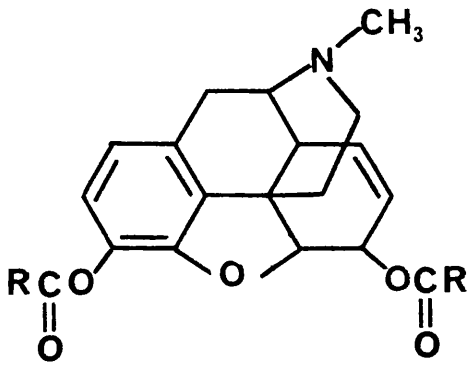
Morphine (1.*1*)

alkaloid and it was soon observed that simpler and effective morphine-like compounds could be prepared which contained only a portion of the parent structure. Efforts in this direction have led to the following classes of analgesics: morphinans, benzomorphans, 4-aryl-piperidines, 4-anilino piperidines, and diphenylpropylamines. All of these classes, along with many other miscellaneous analgesics which cannot be easily classified, will be discussed briefly. A further

group of analgesics, the oripavines first discovered by Bentley and Hardy[3], are more complex than morphine and would not be discussed.

Derivatives of Morphine

Early attempts to find substitutes for morphine involved chemical modification of the naturally occurring alkaloid especially the chemically amenable ring C. Esterification or etherification of the hydroxyl groups of morphine (1.*1*), gave compounds with reduced analgesic activity except in the case of heroin (1.*2*).

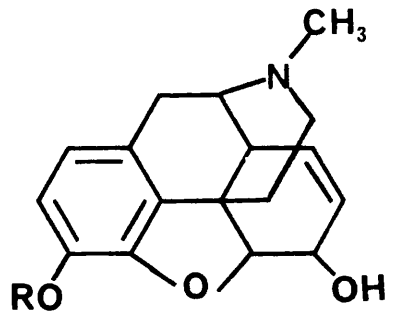


(1.*2*) R = CH_3

(1.*3*) R = H

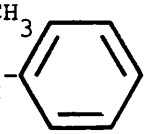
(1.*4*) R = CH_2CH_3

Diacetylmorphine (heroin, 1.*2*), first prepared by Wright[4] was introduced into clinical use as a morphine substitute, but was soon withdrawn in most countries because of its relatively high addiction liability. The "active" species is considered to be 6-acetylmorphine[5]. Other lower and higher acyl homologues (1.*3* and 1.*4*) have since been shown to have similar analgesic potencies and high physical dependence capacity in monkeys[6]. However, typical of the effect produced by masking the phenolic hydroxyl is codeine (1.*5*), an analgesic about 20% as potent as morphine in humans.



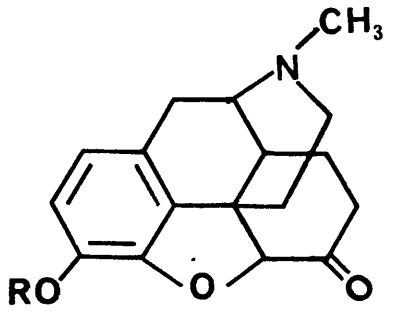
(1.5) R = CH_3

(1.6) R = CH_2CH_3

(1.7) R = $-CH_2-$ 

Codeine is used mainly in the treatment of mild to moderate pain and as a cough suppressant. Other phenolic ethers in clinical use are the ethyl (Dionin^R, 1.6), and benzyl (Peronin^R, 1.7) analogues.

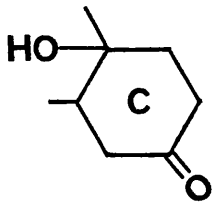
Other chemical modifications to ring C include: oxidation, methylation or replacement by halogen (chloromorphide) of the C-6 hydroxyl group, and the introduction of new substituents such as methyl group in position 5 on ring C. The preparation of compounds incorporating one or more of the above modifications by Small and Eddy[7], have led to several morphine derivatives with enhanced activity. Although none of these derivatives are demonstrably superior to morphine, at least two, hydromorphone (1.8) and hydrocodone (1.9), remain in clinical use in a variety of proprietary analgesic and antitussive preparations.



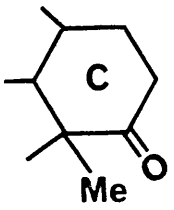
(1.8) R = H

(1.9) R = CH_3

Other examples of useful morphine derivatives include the 14-hydroxy (oxymorphone; 1.*10* partial formula), and 5-methyl (Metopon; 1.*11* partial formula) analogues of hydromorphone.

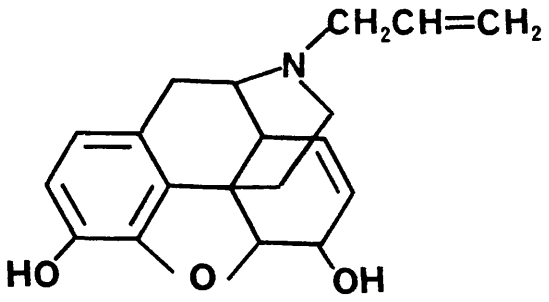


(1.*10*, partial formula)



(1.*11*, partial formula)

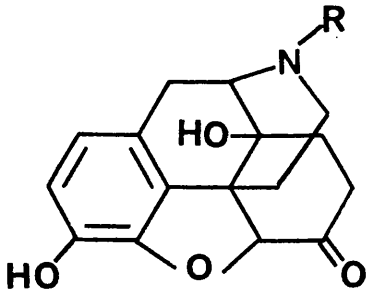
The replacement of the *N*-methyl group of morphine with an *N*-allyl group gave nalorphine (1.*12*), a compound which reversed the actions of morphine in humans[8-10].



(1.*12*)

Although inactive in rodent tests, nalorphine has been shown to possess considerable analgesic potency in primates, and limited dependence producing potential, in human studies. However, its

clinical utility was limited because of the psychotomimetic side effects at analgesic doses. Amongst the other important morphine based antagonists are the *N*-allyl analogue (Naloxone, 1.*13*) and *N*-cyclopropylmethyl analogue (Naltrexone, 1.*14*) of oxymorphone



(1.*13*) R = $-CH_2CH=CH_2$

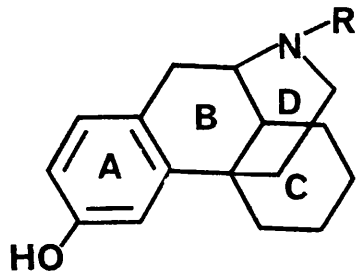
(1.*14*) R = $-CH_2-c-C_3H_5$

These two are pure antagonists because they block the effects of morphine without eliciting any analgesic effects.

Morphinans

The morphinans are a class of compounds lacking the furan oxygen bridge, the alcoholic hydroxyl and the alicyclic double bond of morphine. *N*-methylmorphinan was first synthesised by Grewe in 1946, and was found to be about one-fifth as potent as morphine as an analgesic. The laevorotatory isomer levorphanol (1.*15*) is 4 times as active as morphine, with the same level of addiction liability and is in clinical use today.[11]

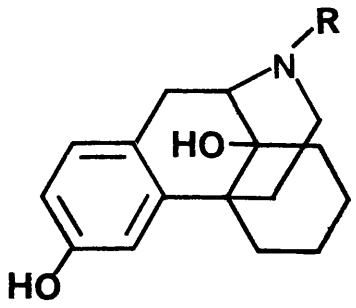
The interest in this class is centred on compounds of the agonist-antagonist type with little or no addiction liability, so



(1.*15*) R = CH_3

(1.*16*) R = $-CH_2$-c-C_3H_5

far considerable success has been achieved. For example, the *N*-cyclopropylmethyl morphinan (cyclorphan, 1.*16*) is a potent analgesic and antagonist without addiction liability[12]. More recently, in the 3,14-dihydroxy morphinans, oxilorphan (1.*17*), and butorphanol (1.*18*), are examples of potent derivatives with agonist and antagonist properties[13,14].



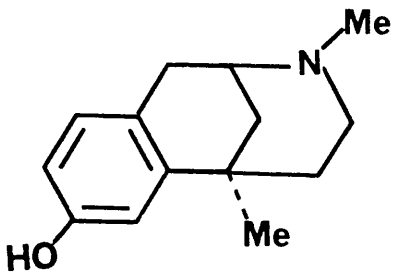
(1.*17*) R = CH_2-c-C_3H_7

(1.*18*) R = CH_2-c-C_4H_9

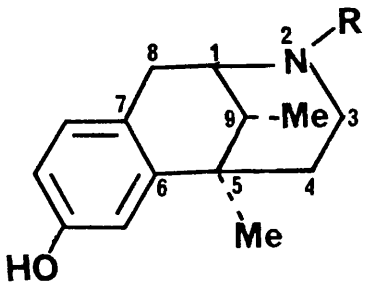
T he former is a strong antagonist with a weak agonist activity and butorphanol is a potent analgesic with moderate antagonist activity[13,14].

Benzomorphans

The benzomorphan class of compounds was first investigated by May and Murphy[15], and the main structural feature is that ring C of morphinans has been excised. The parent compounds in this class are 2'-hydroxy-2,5-dimethyl-6,7-benzomorphan (1.*19*) and the 2,5,9-trimethyl analogue (Metazocine, 1.*20*), structures in which the C-ring of morphinans is replaced by methyl groups.



(1.*19*)



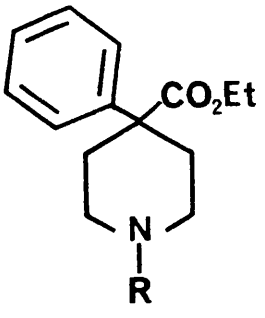
(1.*20*) R = CH_3

(1.*21*) R = $CH_2CH{=}C(CH_3)_2$

The introduction of an extra methyl group at position 9 in (1.*20*) provided a third asymmetric centre and a new stereochemical dimension (possible *cis*- and *trans*-isomerism). In fact, the two possible isomers α-(*cis*) and β-(*trans*)-metazocine have been isolated[16,17]. Several other benzomorphans have been studied and they have been shown to exhibit parallel structure-activity relationships with morphine and the morphinans. In addition, some evidence of separation of analgesic and dependence producing effects in isomers (both diastereoisomeric and enantiomeric; see Chapter 2) was observed in this series[18]. The *N*-dimethylallyl analogue of metazocine (pentazocine, 1.*21*) is in clinical use. A full discussion of the chemistry and structure-activity relationships in the 6,7-benzomorphans follow in Chapter 2.

4-Arylpiperidines

The 4-arylpiperidine class owes its existence to the serendipitious discovery[19] of meperidine during studies of analogues of atropine. In retrospect, it was found to be a further simplification of the morphine molecule. Meperidine (pethidine, 1.*22*) is a narcotic analgesic used mostly for the relief of labour pain[21].



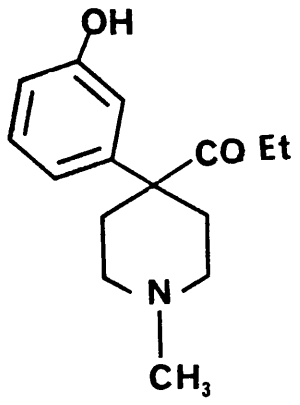
(1.*22*) R = CH_3

(1.*23*) R = $-CH_2CH_2-C_6H_4-NH_2$

(1.*24*) R = $-(CH_2)_5-NHPh$

Like heroin, it was initially thought to be non-addictive, but its dependence liability has since been established in animals and humans[22]. Despite this, it is still one of the most widely used substitutes for morphine in moderate to severe pain situations. Other analogues of pethidine in clinical use include, Anileridine [23] (1.*23*) and Piminodine[24] (1.*24*).

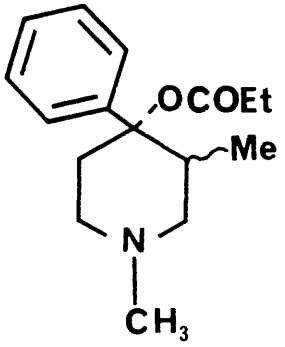
The replacement of the 4-carbethoxy (CO_2Et) group of pethidine with a ketone moiety gave the bemidone series. An example is keto-bemidone (1.*25*), an analgesic twice as potent as pethidine and capable of much greater abuse[25].



(1.*25*)

Replacement of COOEt in pethidine with a propionoxy group (OCOEt) gave the reversed esters of pethidine, which are again highly potent compounds[26]. A typical example is α-prodine (*trans* 3-Me | 4-Ph, 1.*26*) used clinically in obstetrics because of its rapid onset and short duration of action[27].

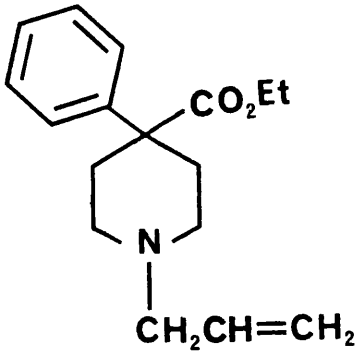
Unlike morphine, the 6,7-benzomorphans and the morphinans, attempts to prepare narcotic antagonists in the 4-aryl piperidine



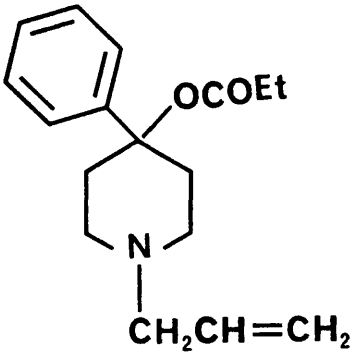
(1.*26*)

series by introducing *N*-substituents such as allyl and cyclopropyl-methyl groups was unsuccessful.

Examples include the *N*-allyl derivatives of norpethidine (1.*27*) and norprodine (1.*28*), which are agonists with no power to block the opiate receptor[28].

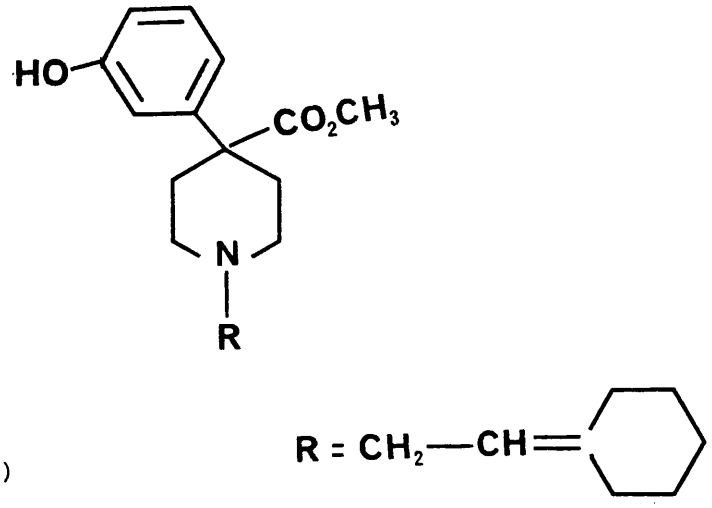


(1. *27*)



(1.*28*)

However, a notable exception to this observation is the methyl ester analogue of bemidone (1.*29*) where antagonists have been so produced[23].



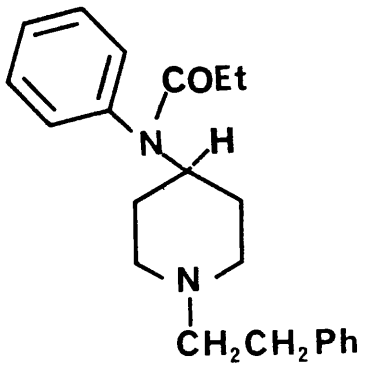
(1.29)

Most of the work undertaken on this class of analgesics has been on the reversed esters because of their high potency. Several reviews on these investigations are available, particularly on the stereochemical structure-activity relationships of the various piperidine ring C-alkylated derivatives[29,30].

4-Anilinopiperidines

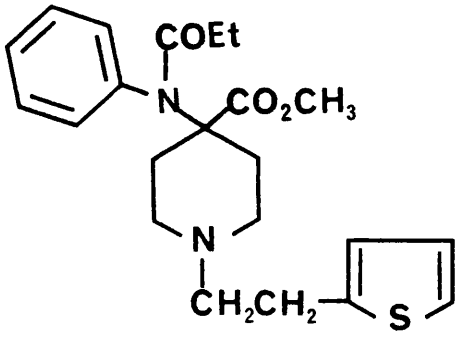
The prototype member of the 4-anilinopiperidine is the highly potent analgesic, fentanyl (1.30)

Fentanyl is a narcotic analgesic with morphine-like actions in mice and respiratory depression in cats and dogs[31]. Due to its rapid onset and short duration of action, it is used in neuroleptanalgesia and in surgical analgesia when given with a major tranquilizer such as droperidol[29]. Structure activity relationships



(1.30)

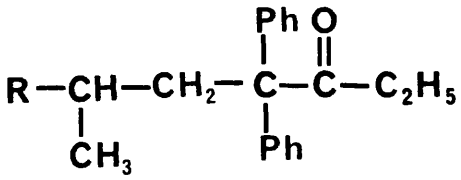
studies of this class by Casy and others, have shown that the *N*-phenethyl group is essential for activity[32]. This finding distinguished the class from the 4-phenylpiperidines where activity is still high in the *N*-CH_3 analogues. In addition, the class has been shown to differ from morphine and the benzomorphans by the demonstration of significant agonist activity in the *N*-allyl and substituted allyl analogues. Other fentanyl derivatives substituted at the 4-position by carboalkoxy (CO_2R) as in pethidine, alkoxymethyl (CH_2OR) and oxoalkyl (COR) as in ketobemidone, have been reported[33]. The most interesting of these analogues is sufentanyl (1.31), which displays high analgesic potency, a short duration of action and an apparently unusual high safety margin.



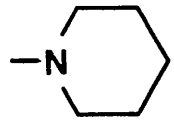
(1.*31*)

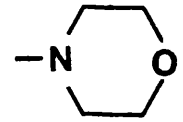
3,3-Diphenylpropylamine derivatives

The ultimate structural simplification of morphine was achieved with the synthesis of methadone, (1.*32*), an open chain analgesic[34].



(1.*32*) R = $-N(CH_3)_2$

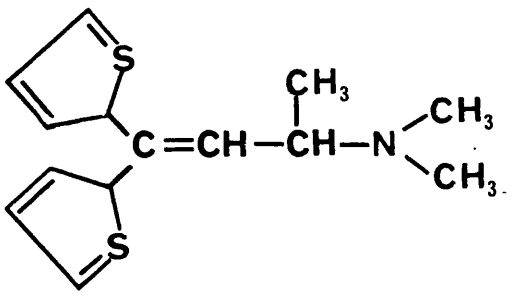
(1.*33*) R = 

(1.*34*) R = 

Methadone is as potent an analgesic as morphine but still has the same side effects, notably respiratory depression and dependence liability[35]. However, because of its oral effectiveness and less severe withdrawal symptoms compared to morphine, it has wide application in the treatment and rehabilitation of morphine and heroin addicts[36]. Other members still in clinical use are the piperidino-analogue (Dipipanone, 1.*33*) and the morpholino-analogue (Phenoxadone, 1.*34*)[36,37].

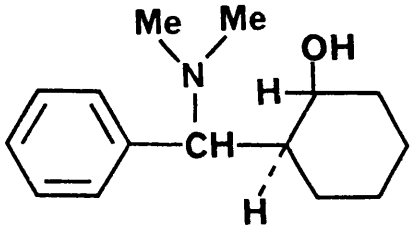
Miscellaneous groups

There are several other interesting structures with opiate activity which do not fit clearly into any of the above classes. Examples include the thiambutenes, represented by 3-dimethylamino-1,1-bis(2-thienyl)-1-butene (1.*35*), a morphine-like analgesic less effective than morphine in humans, but with the same level of abuse liability[38] and the benzylamines, typified by (-)-*cis*-2-



(1.*35*)

(dimethylamino-*m*-hydroxybenzyl) cyclohexanol (1.*36*), which is twice as potent as morphine as an agonist and about equal to nalorphine as an antagonist in rats[39].



(1.*36*)

Unfortunately, despite the vast number of synthetic analgesics prepared, the goal of obtaining an analgesic without the dependence - producing, and other undesirable side-effects of morphine remains elusive. In those agents where a degree of separation between analgesia and dependence is observed, other side effects, such as respiratory depression, still express themselves. Consequently, interest in the whole field of analgesics remains as intense now as it has been at any time in the last twenty years.

1.3 The Opiate Receptor

The term "opiate receptor" is used to designate areas in the brain and peripheral tissues having specific affinity for opiate agonists and antagonists, and thus eliciting a pharmacological response. Long before the unequivocal demonstration of the existence

of the opiate receptor, the circumstantial evidence in favour of their existence was substantial[40,41]. Such evidence was obtained from structure-activity relationship (SAR) studies and includes:-

a) The overall similarities in the nature of opiate agonists, typified by the presence of an aromatic group and a positively charged nitrogen atom capable of ionic bonding, all suggestive of an interaction with a chemically and geometrically complementary site.

b) The stereospecificity of agonists, both pharmacological and steric, in particular a discrimination between the dextrorotatory (d-) and laevorotatory (l-) isomers.

c) The effects of slight structural changes that can convert agonists into antagonists capable of abolishing the analgesic and all other effects of the agonist.

The direct identification of the receptor sites remained elusive for some time, whilst the results from the SAR studies were used to speculate on the nature of opioid receptor(s) and encouraged the proposal of models for the binding of opiates to the receptor. An example of this is the classical studies of Beckett and Casy[42]. In this model, a receptor surface was formulated which possessed a flat lipophilic surface binding the aromatic ring, a cavity to accommodate the hydrocarbon portion of the piperidine ring, and an anionic amine binding site. However, this concept of a 'rigid' receptor was subsequently modified by Portoghese[43] to envisage a receptor with a degree of flexibility in which 'induced fit' is a major factor in opiate-receptor interactions.

More refined models have been proposed which contain an additional lipophilic binding site, designed to rationalise the superior potency of oripavines and fentanyl-related analgesics[44,45]. More recently, the addition of a different loci for amine binding has emerged to accommodate agonist and antagonist receptor states[46,47].

Efforts directed towards identifying the opiate receptor achieved some breakthrough with the proposal of stereospecific binding by Goldstein in 1971[48]. Along with several other workers,[49,50] he demonstrated the existence of an opiate receptor in the midbrain and peripheral nervous tissues of vertebrates, which is capable of stereospecifically binding morphine, other potent agonists,and antagonists such as naloxone. The presence of opiate receptors in the intestine has also been demonstrated, and at the subcellular level opiate receptors are confined specifically to synaptic membranes[51]. Further attempts to characterise the opiate receptor, though unsuccessful, led to the suggestion of the presence of a thiol residue at, or near, the receptor[52].

The identification of the opiate receptor allowed a direct examination of opiate-receptor interactions. The bindings observed in the guinea pig ileum, rat brain and cell cultures of neuroblastoma x glioma hybrids have been correlated with pharmacological activity of both agonists[53] and antagonists[54]. The differences observed in the *in vitro* binding of agonists and antagonists in the presence of sodium ions has led to the proposal of the allosteric model of the opiate receptor[55,56]. This model presumes that the opiate receptor can assume two different conformations, and that sodium ion plays a crucial role in effecting a transition between the two states[57].

The antagonist is presumed to act on the sodium bound form, and the agonist on the non-sodium bound form, to elicit their respective actions. This theory explains the *in vivo* superiority of antagonists over agonists, but leaves a number of questions unanswered. Based on binding studies and further pharmacological evidence, however, the possible existence of further discrete and non-interconvertible receptors has been proposed[58].

The demonstration of the existence of opiate receptors in the nervous system and peripheral tissues raised questions about the functions they serve, as it is clear that receptors do not exist in the body for the sole purpose of receiving exogenous drugs. The quest for a rational explanation for their existence inspired an intensive research effort which, in 1975, culminated in the demonstration in pig brain extract[59,60] and human cerebrospinal fluid[61] of endogenous opioid substances. Hughes *et al.*[62] subsequently isolated from the brain of pigs, two related pentapeptides which they named enkephalins.

The two peptides have the same amino acid sequence but differ only in their C-terminal amino acid residue, these being methionine (Met-enk., 1.*37*) and leucine (Leu-enk., 1.*38*).

Tyr-Gly-Gly-Phe-Met

1 2 3 4 5

(Met-enk., 1.*37*)

Tyr-Gly-Gly-Phe-Leu

1 2 3 4 5

(Leu-enk., 1.*38*)

Met-enk. is a potent agonist in the mouse vas deferens (x20 normorphine) and the guinea pig ileum (x1 normorphine) tests , both activities being completely reversed by naloxone. Leu-enk exhibits a similar profile of activity but is less potent. The enkephalins have a short duration of action compared to morphine[63] due to metabolic lability, as evident from rapid denaturation by tissue homogenates[59,64].

The recognition that Met-enk. was identical to the fragment 61 - 65 of the pituitary hormone β-lipotropin (β-LPH) led to an extensive examination of the pituitary extracts for opiate activity and this led to the isolation of high molecular weight peptides, the endorphins[65,66]. Three of these polypeptides have been isolated: α-endorphin (β-LPH$^{61-76}$), β-endorphin (β-LPH$^{61-91}$) and γ-endorphin (β-LPH$^{61-77}$). Of these, only the α and β endorphins have analgesic activity, with β-the more active of the two. β-endorphin has been shown to be 3x more active than morphine when injected intravenously, and its effects are blocked by naloxone[67]. In contrast to the enkephalins, however, β-endorphin is relatively stable to brain peptidases. The influence on activity of the C-terminal tetrapeptide (Lys_{88} - Lys_{89} - Gly_{90} - Glu_{91}) of β endorphin has been studied. The removal of residues 90 and 91 had little effect, whilst removal of residues 88 and 89 (Lys-Lys) had a profound effect on opiate activity as measured by binding to brain synaptosomal membranes and tail flick assays in rats[68].

The idea that structures based on natural opiates might avoid the physical dependence and tolerance inherent in narcotic analgesics has stimulated considerable interest in synthetic analogues of enkephalins. Unfortunately, however, both Met-enk. and β-endorphin

were shown to cause typical opiate withdrawal symptoms after chronic infusions into rat brain[69,70].

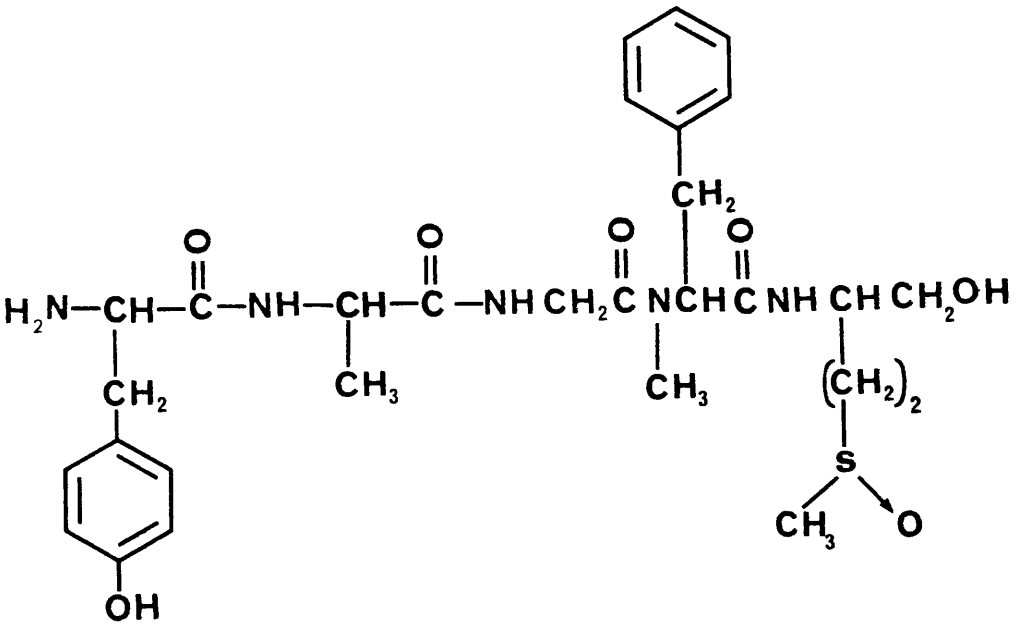
Nevertheless, a number of structure-activity relationship studies have been carried out on the enkephalins. The need for a correct absolute stereochemistry (L) for tyrosine (Tyr^1) has been demonstrated. Replacement with D-Tyrosine as in ($D\text{-}Tyr^1$)-Met-enkephalin led to loss of opiate activity in the receptor binding studies and vas deferens assay[71]. The importance of the free phenolic and amino groups of tyrosine have also been demonstrated. The des-amino Tyr-analogues of Met- and Leu-enkephalins were inactive[72], and removal of the -OH group of the tyrosine residue had a pronounced adverse effect on activity[73]. Masking of the tyrosine amino group by *N*-carbamylation or Tyr-OH by *O*-benzylation similarly abolished or reduced the opiate properties of β-endorphin.

Since the primary mode of degradation of enkephalins has been shown to be the cleavage of Tyr-Gly amide bond,[74,75] increased resistance to enzymatic degradation has been achieved by substituting a D-amino acid for glycine at the 2-position, and also by forming the amide at the carboxylic acid terminal of methionine[76].

For example, the $D\text{-}Ala^2$-enkephalin derivative was particularly resistant to peptidyl enzymes while retaining the properties of the natural enkephalin[77].

Other stable synthetic analogues of Met-enk. with longer duration of action and increased potency were obtained by altering the terminal

Met-COOH to CH_2OH (Met^5-ol) substituting Gly^2 by D-Ala, oxidation of Met. sulphide to sulphoxide, and *N*-methylation of the Phe^4-residue[78]. The peptide with D-Ala^2-Met^5-ol sequence showed subcutaneous (s.c.) activity as well as prolonged intravenous (i.v.) analgesic potency. The compound (1.*39*) incorporating all the changes D-Ala^2-MePhe^4-Met-(O)^5-ol showed analgesic activity even after oral administration and was many times more active than Met-enk. and morphine in mice following i.v. injection.



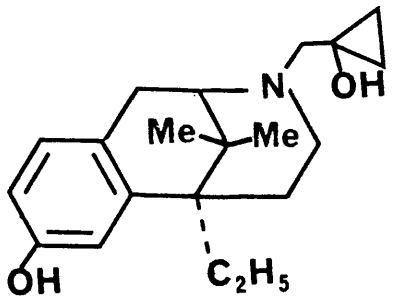
(1.*39*)

Though the goal of producing structures based on endogenous opioids without physical dependence and tolerance inherent in narcotic analgesics has not been achieved, analogues of peptide opioids have been invaluable in studying both the central and peripheral actions of analgesics, mapping distribution of opiate receptors in various tissues and in defining the diverse roles now known to be associated with the enkephalins and endorphins *vis á vis* other narcotic analgesics.

Concept of multiple receptors

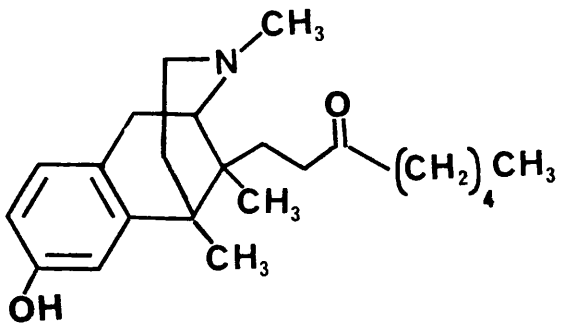
The different pharmacological profile observed with a wide variety of narcotic analgesics (peptide and non-peptide) gave rise to the hypothesis of the existence in the brain of multiple opiate receptors (putative δ, μ, κ, ε, and σ)[79,80]. Such a concept might help to explain the roles played by the enkephalins and endorphins, and tentatively provide explanations for some anomalous pharmacological observations with opioid peptides. For example, the concept helped to explain why the potency of naloxone as an antagonist of morphine is comparable to that of enkephalin in the mouse vas deferens but not in the guinea pig ileum[81].

Extensive competitive binding assays in guinea pig brain homogenate[82], along with comparative pharmacology in the guinea pig ileum assay and mouse vas deferens assay[83], gave compelling evidence for at least two distinct receptors: μ (morphine) and δ (enkephalin). More recent studies suggest the existence of two further receptor entities: the ε, proposed for the opiate receptor in the rat vas deferens with pronounced selectivity for β-endorphin[84,85], and, κ-receptor for which bremazocine (1.40) is an agonist[86].



(1.40)

Several research workers have studied specific responses mediated by each opiate receptor. Reports[87,88] suggest that μ and/or κ-receptors are responsible for analgesic effects, while δ and σ receptors mediate other effects. The prototype agonists for these receptors are, morphine (μ), ketocyclazocine (κ) and *N*-allylnorcyclazocine (σ). Naloxone is the prototype μ-antagonist and the novel benzomorphan (1.*41*) is a selective κ-antagonist. No selective σ-antagonist is known to date.



(1.*41*)

This characterisation of receptors and the ligands with which they possibly interact has helped to explain some of the different pharmacological profiles noticed for opiates (peptides and non-peptides). For example, Hutchinson *et al.*[89] have noticed in a study of certain benzomorphans that an enhanced guinea pig ileum/mouse vas deferens potency ratio, coupled with poor reversal of activity by naloxone, is predictive of interactions at the κ receptor and, hence, a low morphine-like dependence liability.

The demonstration and location of opiate receptors, and the

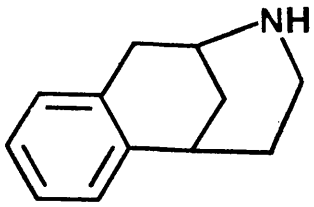
ligands with which they interact (the enkephalins and endorphins), was a milestone in analgesic research. It provides not only a rational explanation for some hitherto unexplained pharmacological observations, but promises an understanding of the mystery of tolerance and dependence. Though attempts to obtain the 'ideal' analgesic based on the endogenous opiates has been unsuccessful, there is hope that further studies with both synthetic and endogenous opioids will lead ultimately to accurate dissection of opioid pharmacology and structure activity relationship thereby leading to analgesics with enhanced selectivity of action.

CHAPTER 2

Chemistry and Structure-Activity Relationships of 6,7-Benzomorphans

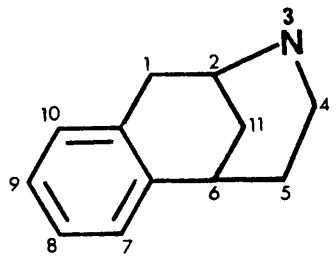
2.1 Nomenclature

The preparation of the first compound containing the benzomorphan ring system (2.*1*), was reported by Barltrop in 1947[90].

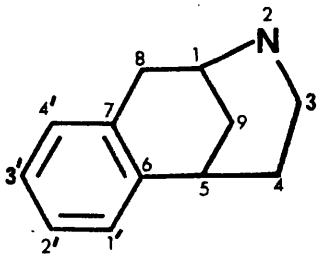


(2.*1*)

There are two common numbering systems for the parent ring of benzomorphans. 1,2,3,4,5,6-Hexahydro-2,6-methano-3-benzazocine, (2.*2*), as described in the "Ring Index" and Chemical Abstracts; and 6,7-benzomorphan (2.*3*), the nomenclature suggested by Barltrop and adopted by Eddy and May[91].



(2.*2*)



(2.*3*)

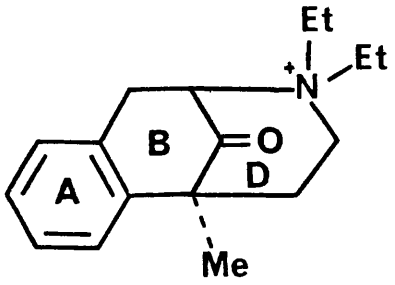
The latter will be used throughout this thesis.

2.2 Synthesis and Stereochemistry

The various synthetic approaches to 6,7-benzomorphans have been extensively reviewed[91,92]. The two most important routes, the tetralone route and Grewe's cyclisation are briefly discussed, highlighting the advantages and disadvantages of their use. A brief mention will be made of other routes.

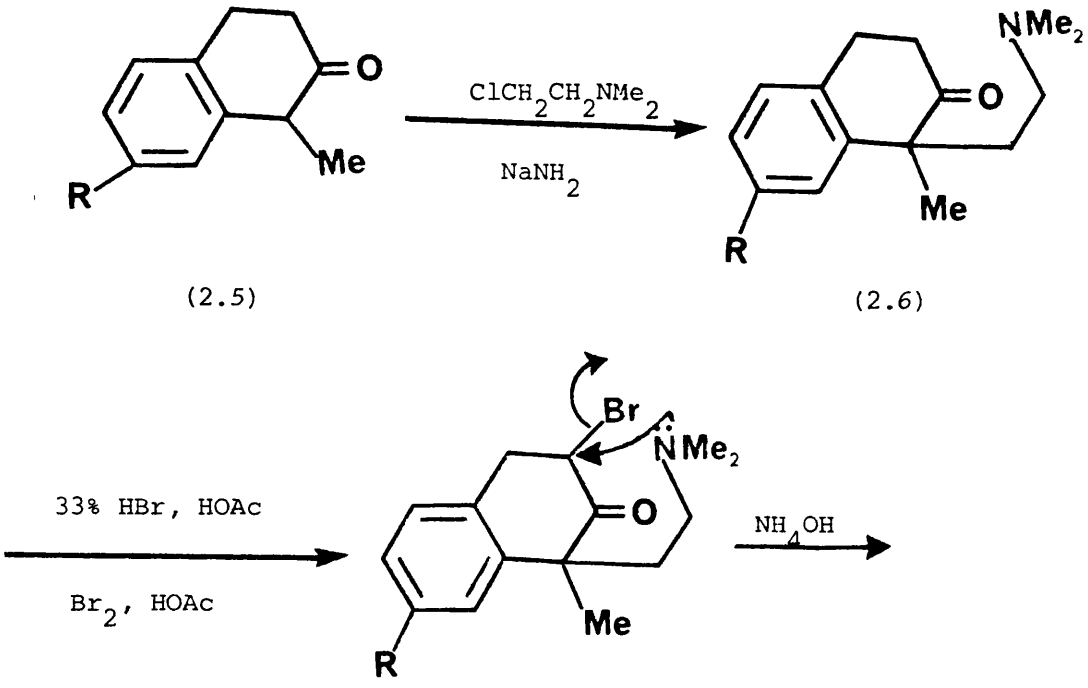
The tetralone routes

The application of this route to the synthesis of 6,7-benzomorphans followed the initial work of Barltrop[90] in the synthesis of (2.4), as a model for A, B and D rings of morphine (1.1)



(2.4)

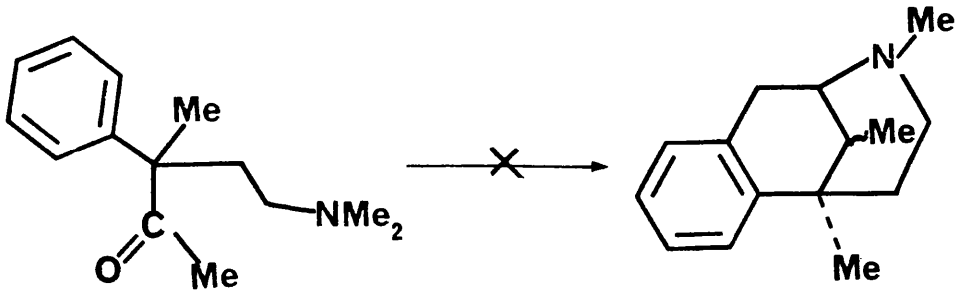
Following his method, May[15] prepared 2,5-dimethyl-6,7-benzomorphan


ClCH2CH2NMe2
NaNH2
NMe2
O
Me
R
(2.5)
(2.6)
33% HBr, HOAc
Br2, HOAc
Br
NMe2
NH4OH
(2.7)
Me Br⁻
Me
N⁺
(1) dry distil
(2) HCl
(3) 95%
H2NNH2,KOH
N
(2.8)
(R = H; 2.9a)

SCHEME 1

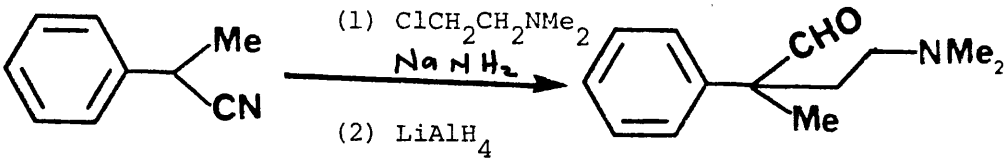
(2.9a) (Scheme 1). Alkylation of 3,4-dihydro-1-methyl-2(1H)-naphthalenone (2.5), with β-dimethylaminoethyl chloride gave (2.6), which was brominated and cyclised in base to the methiodide (2.8). Dry distillation and reduction of (2.8) afforded the benzomorphan (2.9a). The overall yield was, however, very poor due to the low yields of some of the reaction steps in the sequence; for example, (2.8) → (2. 9).

Alternatively, a longer, but higher yield, route starting with 2-phenylpropionitrile (2.10) was used. (See Scheme 2). In this scheme, 2-phenyl propionitrile was converted into the tetralone (2.13), which was sequentially converted to the benzomorphan (2.9a) in 5% yield. However, the use of the tetralone route is limited largely to the preparation of 5-substituted benzomorphans[93-95], as attempts to prepare the trimethyl derivatives have been unsuccessful[96,97]. For example, the key aminoketone (2.15), in the preparation of 2,5,9-trimethyl-6,7-benzomorphan (2.16), was unreactive under Knoevenagel conditions with either malonitrile or methyl cyanoacetate[98].

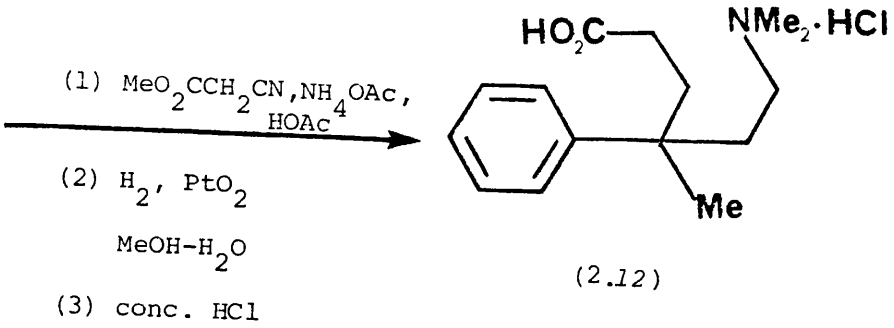


2.15 2.16

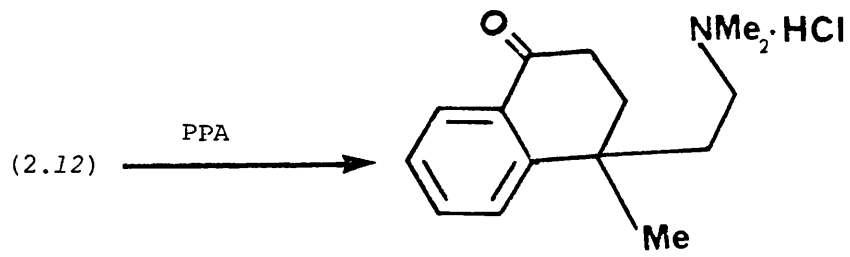
In addition, a change of the alkylating chloroalkylamine to 1-chloro-



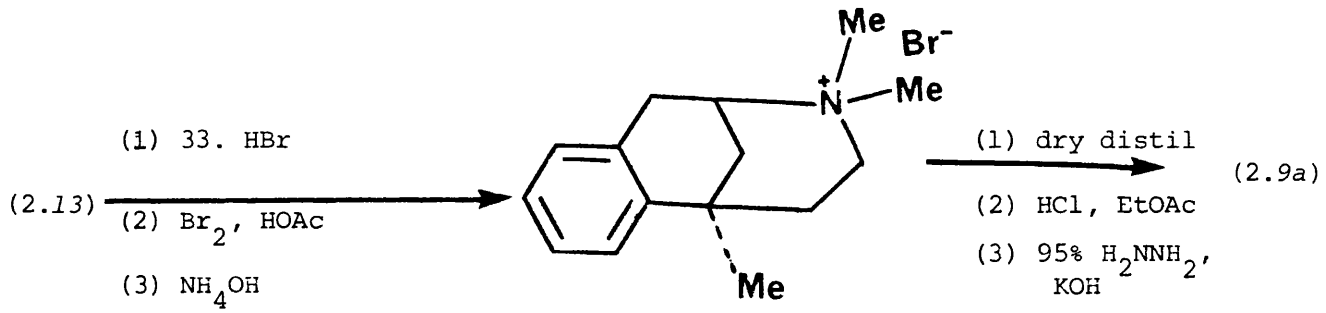
(2.*10*) (2.*11*)



(2.*12*)



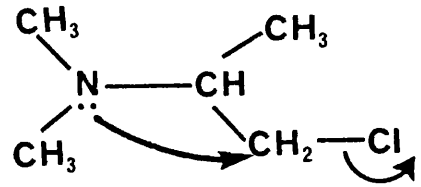
(2.*13*)



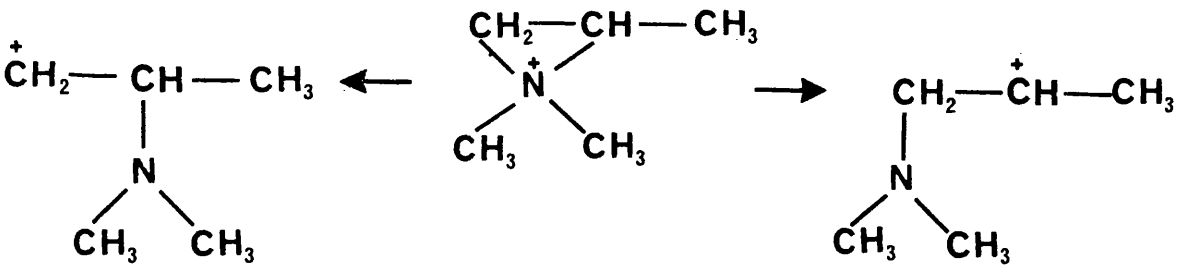
(2.*14*)

SCHEME 2

2-dimethyl-aminopropane (2.*17*), in the attempted preparation of 2,3,5-trimethyl-6,7-benzomorphan, affected the nature and yield of the products due to the formation of two carbonium ion species. (see Scheme 3). Thus, 1-chloro-2-dimethylaminopropane in the base form cyclises to the quaternary salt (2.*18*). The carbonium ion species from (2.*18*) is a mixture of (2.*19*) and (2.*20*) which affects the alkylation stages. Reaction of these ions with the sodium salt of (2.5) will lead to a mixture of products and low yields. This has in fact been found to be the case[97].



(2.*17*)

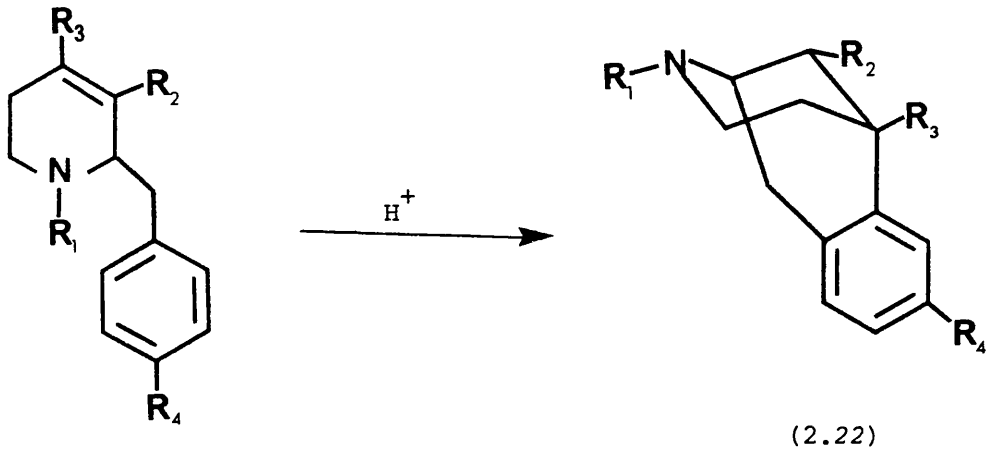


(2.*19*) (2.*18*) (2.*20*)

SCHEME 3

The Grewe Method

This method is analogous to Grewe's synthesis of morphinans, and is based upon the acid catalysed cyclisation of appropriately substituted tetrahydropyridines[99,100]. For example, (2.*21*) to (2.*22*)



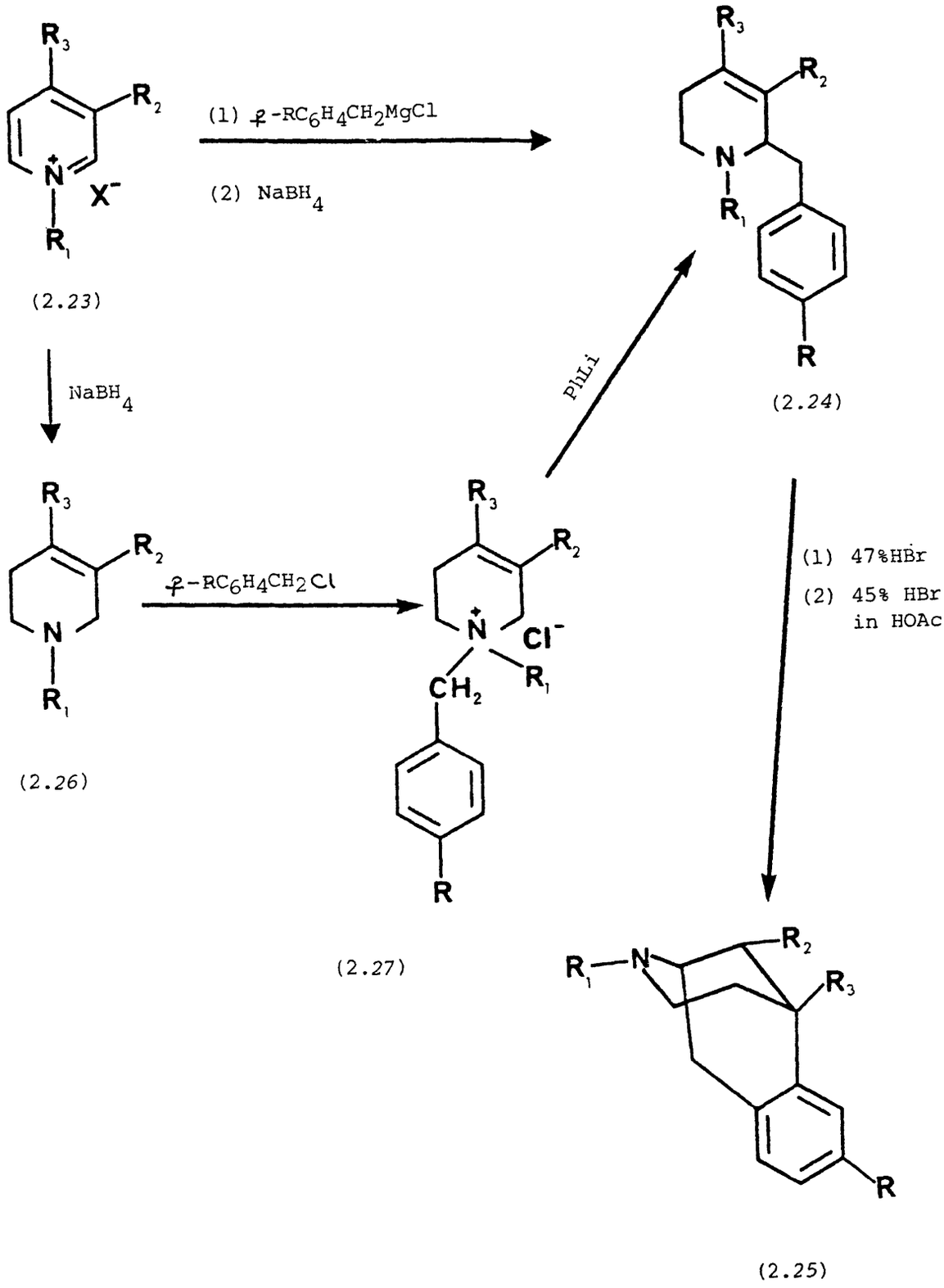
(2.*21*) (2.*22*)

The tetrahydropyridine precursor may be obtained in either of two ways:

a) from the reaction of an appropriate Grignard reagent with a pyridinium salt; and

b) *via* a Steven's rearrangement of the corresponding benzylalkyl-pyridinium salts[101].

In the former (see Scheme 4), the benzyl Grignard reagent is added to the pyridinium salt (2.*23*), to give an unstable dihydropyridine which, on immediate reduction, affords the tetrahydropyridine (2.*24*). Acid catalysed cyclisation yields the benzomorphan (2.*25*). The Steven's rearrangement involves sodium borohydride reduction of the



(2.23) (2.24) (2.26) (2.27) (2.25)

SCHEME 4

1,3,4-trialkylpyridinium salt (2.*23*) to the tetrahydropyridine (2.*26*), which is then quaternised with an appropriate benzyl halide to give the tetrahydropyridinium salt (2.*27*). Rearrangement of (2.*27*) is effected with phenyl-lithium to give the tetrahydropyridine (2.*24*) which is cyclised in acid to the benzomorphan (2.*25*). The product(s) from the Steven's rearrangement, steps (2.*27*) → (2.*24*), is dictated by the stability of the ylide intermediate.

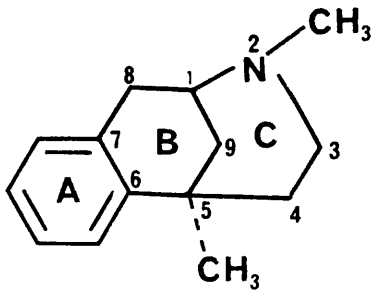
The Grewe route is highly versatile, as the nature and positions of the R groups can be varied. In fact, a wide variety of substituted benzomorphans have been prepared by this route.[17,102-104]. Although the Grewe route is extremely useful, it suffers, in certain instances, from difficulties in preparing the required alkylpyridines.

There are several other routes for preparing benzomorphan structures with specific substitution which are not yet developed into generally useful methods.These include: piperidinol and related cyclisations[105,106], Beckmann rearrangement reactions[107], *meta*-bridging[108] and straightforward modification of substituents on the benzomorphan ring by classical reactions, such as alkylation, acylations, etc.

Stereochemistry of 6,7-benzomorphans

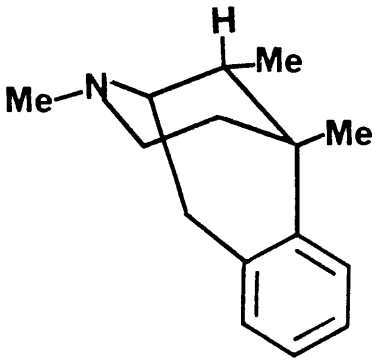
From an examination of models, it may be demonstrated that the aminoethyl bridge in 6,7-benzomorphans must be *cis*-fused to the tetrahydronapthalene skeleton, the *trans*-isomer being too severely strained to be thermodynamically possible. Thus, the 5-substituent

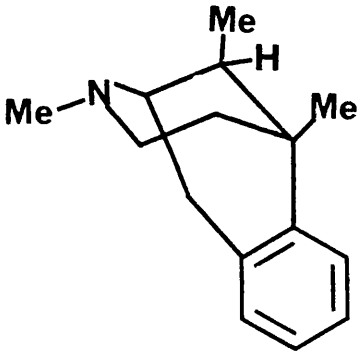
(2.9*a*) is in a *trans*-configuration to the 1,2-bond. However, the introduction of an alkyl group into any other position in the piperidine



(2.9*a*)

ring C of 2,5-dimethyl-6,7-benzomorphan (2.9*a*), introduces a new stereochemical dimension. That is, an added *cis*-/*trans*-isomerism. The stereochemistry of these substituents could be related to either the hydroaromatic ring B, or the piperidine ring C. For example, the Grewe synthesis of 2,5-9-trimethyl-6,7-benzomorphan (2.26*a*) and (2.27*a*) yields principally the product (2.26*a*) where the methyl groups at C-5 and C-9 are *cis*- with respect to the hydroaromatic ring B, (*trans*- with respect to the piperidine ring C) and designated by May and Eddy as $\underline{\alpha}$[91]. Small quantities of the minor isomer, designated $\underline{\beta}$-, where C-5 and C-9 methyl groups are *trans*- with respect to the hydroaromatic ring (and *cis*- with respect to the piperidine ring) have also been isolated. Both methods of isomer designation will be utilized in the course of this work.





α -*cis*

β-*trans*

(2.26*a*)

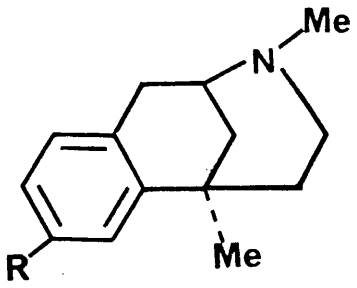
(2.27*a*)

2.3 Structure-Activity Relationships in 6,7-Benzomorphans

Since the preparation of 2'-hydroxy-2,5-dimethyl-6,7-benzomorphan (R = OH, 2.9), by May and Murphy[15], much time and energy has been devoted to synthetic variation of the 6,7-benzomorphan nucleus. Analgesics showing separation of analgesic and physical dependence characteristics have been produced[18,91,109], and many interesting if somewhat puzzling, structure-activity relationships revealed. A brief review of the structure-activity relationships in the 6,7-benzomorphan series will now be presented, with emphasis on ring substituents and stereochemical aspects.

2.3.1 A-ring modifications

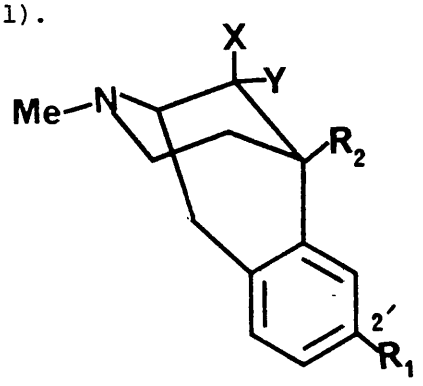
The introduction of a phenolic hydroxyl group at the 2'-position of 6,7-benzomorphans yields compounds with enhanced analgesic potency and reduced toxicity compared to the unsubstituted analogues[110,111]. For example, 2'-hydroxyl-2,5-dimethyl-6,7-benzomorphan (R = OH, 2.9).



(2.9)

	ED_{50} (mg/kg)
R = H,	11.0
R = OH,	3.3
R = $OOCCH_3$	3.1
Morphine	2.4

Acetylation of a benzomorphan 2'-hydroxyl group further increases analgesic potency: 2'-acetyl-2,5-dimethyl-6,7-benzomorphan (R = $OOCCH_3$, 2.9) compared with 2'-hydroxyl-2,5-dimethyl-6,7-benzomorphan (R = OH, 2.9). The replacement of either the 2'-H or 2'-hydroxyl group with nitro, amino or halo groups in 5,9-dialkyl-2-methyl-6,7-benzomorpans (2.28) gave compounds with diminished analgesic potency and increased toxicity, as determined by the mouse hot plate test[112] (see Table 1).



(2.28)

α X = H, Y = R_3

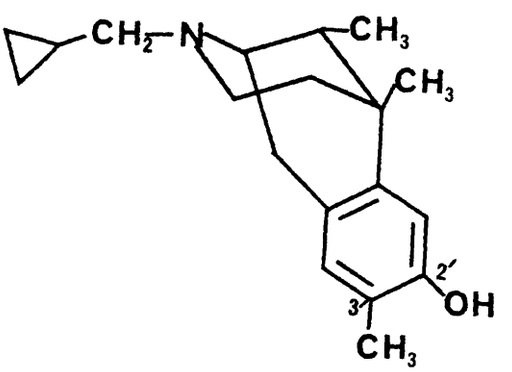
β X = R_3, Y = H

Table 1.[112] Comparison of analgesic activity of 2'-substituted benzomorphans[a]

Entry	2-methyl-6,7-benzomorphan	ED_{50} (mg/kg) s.c.
1	α-5,9-Diethyl-	2.5
2	2'-hydroxy-	2.1
3	2'-nitro	9.4
4	2'-amino-(2 HBr)	18.7
5	β-5,9-Diethyl-	2.1
6	2'-hydroxy-	0.2
7	2'-nitro-	25.0
8	2'-amino- (2 HBr)	13.2
9	β-5,9-Dimethyl- (HBr)	2.5
10	2'-hydroxy	0.3
11	2'-nitro	11.1
12	α-5,9-Dimethyl-	13.5
13	2'-hydroxy	1.2
14	2'-chloro	47.0
15	2'-fluoro	22.7
16	Morphine	1.2

a. All salts are HCl unless otherwise stated.

This reduction in activity is much more pronounced in the β- than in the α-series (compare entries 1 - 3 and 5 - 7, Table 1). The effects of substitution at the 3'-position of the aromatic ring has

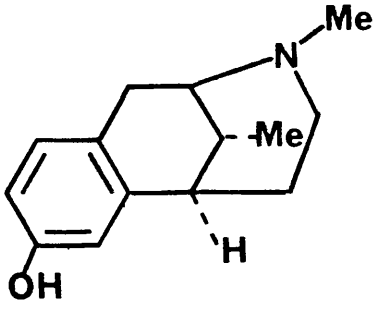


(2.29)

also been studied by Ziering *et al.*[113]. They found that 3'-methyl-benzomorphan derivatives are weakly active in both the mouse hot plate and writhing tests, but, with appropriate nitrogen substituents are good antagonists. For example, N-cyclopropylmethyl analogue (2.29) ED_{50} = >45 mg/kg; AD_{50} = 0.7 mg/kg body weight.

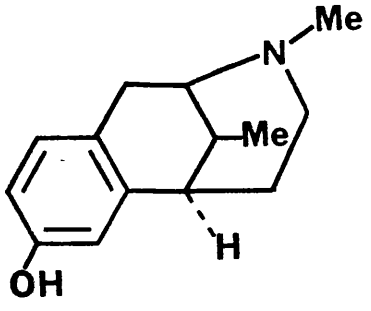
2.3.2 Structure-Activity relationships in compounds bearing B and C ring substituents

Following the successful preparation of 2'-hydroxyl-2,5-dimethyl-6,7-benzomorphan, a series of 5-alkyl and 5,9-dialkyl (α-*cis* and β-*trans*) derivatives of 2'-hydroxyl-2-methyl-6,7-benzomorphan have been synthesised and tested for analgesic activity in mice, and physical dependence capacity in monkeys[95, 115-117]. The results are illustrated in Table 2. These show that the *trans*- (9β)-isomers in the dialkyl homologues are generally more potent than the *cis*-(9α)-isomers (see Table 2; also Section 2.3.4).The same trend has been observed for 9α and 9β analogues of 2'-hydroxy-2-methyl-6,7-benzomorphan lacking a quaternary carbon at C- 5[118]. For example, the 9β analogue (2.30b), of isomeric 2,9-dimethyl-2'-hydroxy-6,7-benzomorphan was 4 times as potent as the 9α-analogue (2.30a) in the mouse hot plate test[119,120].



(2.30a)

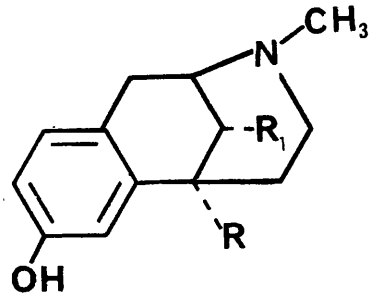
ED_{50} 4.3 mg/kg



(2.30b)

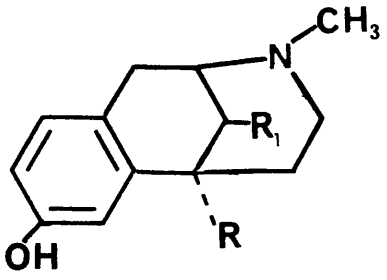
ED_{50} 1.1 mg/kg

Table 2.[114] Pharmacology of (±)-5-alkyl and (±)-5,9-dialkyl-2-methyl-6,7-benzomorphans.



-5-Monoalkyl and α-5,9-dialkyl compounds

Entry	R	R_1	ED_{50}[a]	LD_{50}[a]	Abstinence Suppressant Dose, mg/kg	Physical Dependence Capacity
1	Me	H	10.4	175	2-60, no suppression	None
2	Et	H	2.3	170	1-16, " "	Low
3	Pr	H	2.1	130	3-30, " "	None
4	Me	Me	3.0	175	24, " "	Low
5	Me	Et	1.5	134	2-12, " "	None
6	Et	Me	4.9	309	740, " "	Low
7	Et	Et	4.2	425	2-60, " "	
8	Pr	Me	2.9	>300		
9	Pr	Pr	71.2	>400	3-48, " "	None



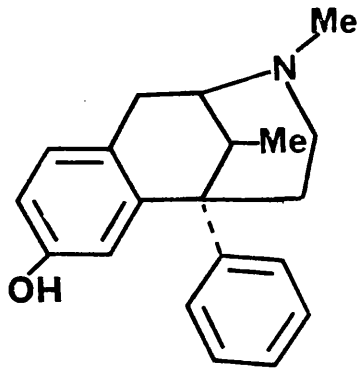
β - 5,9-Dialkyl compounds

10	Me	Me	0.44	67	>18	Low
11	Me	Et	0.47	100		
12	Et	Me	0.27	75	1.0[b]	Intermediate
13	Et	Et	0.28	120	0.5-12 no suppression	None
14	Pr	Pr	0.87	55		
15	Morphine		2.1	550	3	High

Footnote: a. Expressed in mg/kg(mice, subcutaneous administration)
b. All abstinence signs were not uniformly expressed by any dose (to 12 mg/kg) which did not produce some side effects.

The *cis*-compounds in the 5,9-dialkyl, and other 5-monoalkyl,derivatives in the benzomorphan series have little or no ability to substitute for morphine in addicted monkeys. Of the monoalkyl compounds (entries 1-3, Table 2) it can be seen that the 5-ethyl and propyl analogues possess similar levels of analgesic potency which is some 4 to 5 times greater than the 5-methyl compounds. In the α-dialkyl series, maximum activity was shown by the 5-methyl-9-ethyl derivative (entry 5, Table 2), while the 5-ethyl-9-methyl (entry 12, Table 2) proved to be the most effective in the β-series.

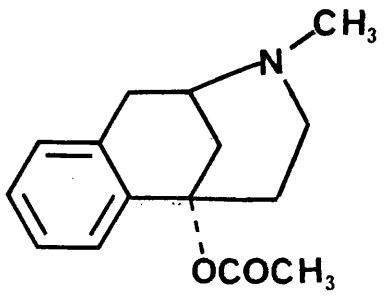
Other 5-substituted benzomorphans have been prepared. 9-methyl-5-phenyl-6,7-benzomorphan (2.*31*), prepared by Clarke *et al.* gave only the 9β-isomer, which is equipotent with β-metazocine (entry 10, Table 2).[121] However, no potent analgesic resulted from the



(2.*31*)

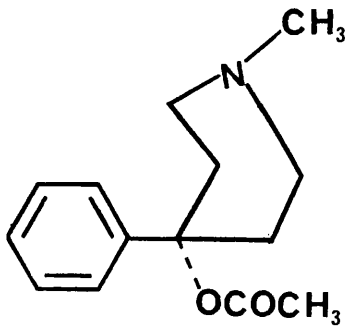
construction of prodine-like benzomorphans (2.*32*)[122]

ED_{50} 5.1 mg/kg



(2.*32*)

ED_{50}[123] 3.6 mg/kg

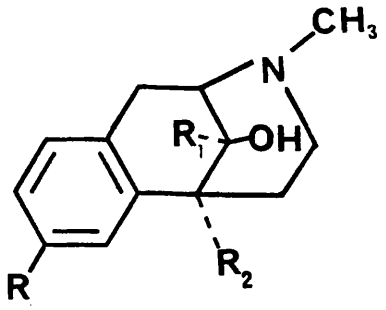


Prodine (2.*33*)

The author will now briefly consider those 5-alkyl and 5,9-dialkyl benzomorphans additionally substituted in position 9. C-9 hydroxylation of 6,7-benzomorphans, a situation comparable to 14-hydroxylation of morphines and morphinans, leads to a decrease in analgesic activity in the *N*-Me compounds. (See Table 3)[124]. Compare the corresponding ED_{50} values in Table 2.

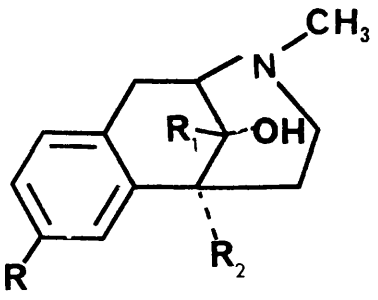
Similar C-9 hydroxylation of benzomorphans bearing antagonist side chain leads to an increase in antagonist activity, in particular, 9β-hydroxylation. For example, 9β-hydroxypentazocine is 3 times more active than pentazocine as an antagonist of pethidine[125]. Janssen[126] reported the effect of the introduction of a second methyl group in the 9α-monomethyl benzomorphan derivatives displaying agonist and antagonist activity. The 9,9-dialkyl compounds(2.*34*) produced are pharmacologically similar, and more potent and longer acting, than the parent compounds.

Table 3.[124] Analgesic activity of 9-hydroxy-6,7-benzomorphans



α-9-OH-6,7-benzomorphans

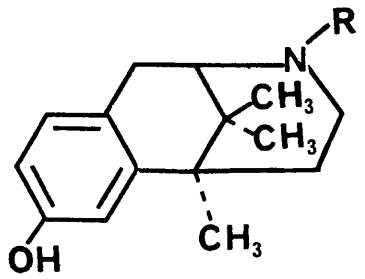
Entry	R	R_1	R_2	ED_{50} mg/kg
1	H	H	Me	63.8
2	H	Me	Me	43.7
3	OH	H	Me	79.9
4	OH	Me	Me	6.91



β-9-OH-6,7-Benzomorphans

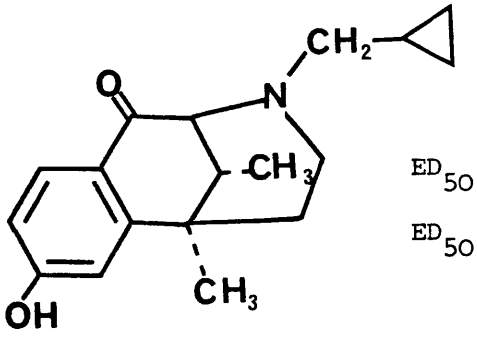
5	H	Me	Me	112.1
6	OH	Me	H	>100
7	OH	Me	Me	6.03
8	Morphine sulfate			2.0

Compounds were tested as HCl or HBr (subcutaneous administration in mice).



(2.34)

Attention is now given to those benzomorphans with alkyl substituents in positions 5 and 9 which also bear a C-8 substituent. The introduction of an oxygen function on the benzylic carbon at C-8 of benzomorphan produces another subseries displaying a varied mix of agonist and antagonist properties[127]. Essentially, carbonyl oxygen at C-8 greatly reduces narcotic antagonist activity, while agonist activity remains unchanged. For example, 8-oxocyclazocine (2.35) is a potent agonist in acetylcholine-induced writhing tests, but a weak antagonist of pethidine (compare both agonist and antagonist activities of cyclazocine, ED_{50} = 0.15 mg/kg; AD_{50} = 0.02 mg/kg).

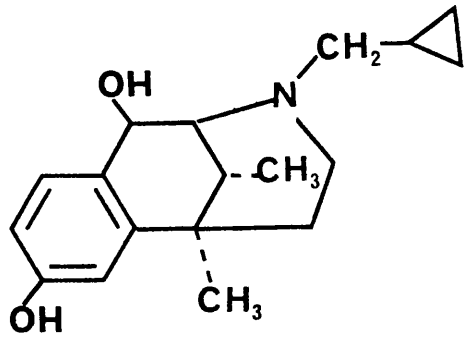


ED_{50} = 0.16 mg/kg

ED_{50} = 7.2 mg/kg

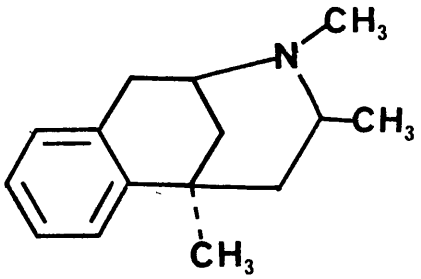
(2.35)

8-Hydroxy-benzomorphans have also been reported, all of which are of low potency either as agonist or antagonist[127,128]. For example, 8-hydroxycyclazocine (2.*36*). (ED_{50} = 10 mg/kg; AD_{50} = 11 mg/kg).



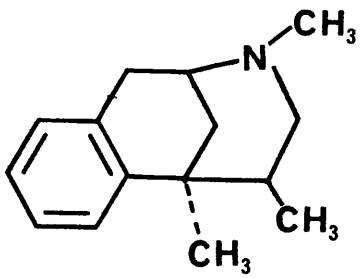
(2.*36*)

Finally, 5-alkylbenzomorphans additionally substituted in positions 3 and 4 have also received some attention. 3- and 4-Methyl benzomorphans (2.*37*) and (2.*38*) respectively have been synthesised and the conformation established[129].



(2.*37*)

ED_{50} = 11.9 mg/kg s.c.



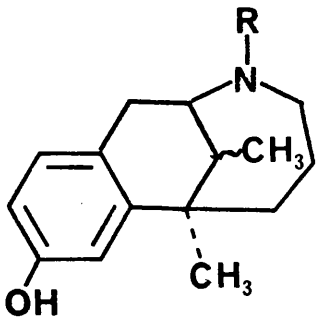
(2.*38*)

ED_{50} = 4.2 mg/kg s.c.

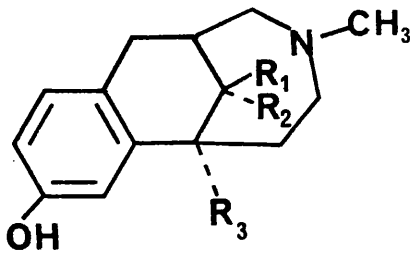
The lower agonist potency (mouse hot plate) of the 3-methyl derivative compared with the 4-methyl analogue has been attributed to the hindrance of the tertiary nitrogen in the former. Also, the higher agonist potency of the 4,5-dimethylbenzomorphan (2.*38*) compared with the 5,9-positional isomer (ED_{50} = 4.5 mg/kg) suggests that the usual positions of dialkyl substitution in the piperidine ring of 6,7-benzomorphan (positions 5 and 9, relating it to the morphinans) may not be optimal regarding activity[129].

Homobenzomorphans

Amongst skeletally modified 6,7-benzomorphans, ring C expanded analogues (homobenzomorphans) of type (2.*39*) and (2.*40*) are most prominent. Compounds of the former type with significant agonist[131] and antagonist[132] activity, depending on the nature of the *N*-substituent



(2.*39*)



(2.*40*)

have been described. Of the latter type, the most potent derivative was (2.*40*, $R_1 = R_2 = CH_3$, R_3 = H) which had a tail flick ED_{50} in mice slightly lower than that of morphine (see Table 4)[130].

Table 4. Analgesic activity of some homobenzomorphan (2.40) derivatives[130].

Entry		ED_{50} s.c. μmole/kg	LD_{50} μmole/kg
1	$R_1 = R_2 = R_3 = H$[a]	10.7	121
2	$R_1 = R_2 = H$; $R_3 = Me$[b]	9.9	184
3	$R_1 = R_3 = H$; $R_2 = Me$[b]	8.0	153
4	$R_1 = Me$; $R_2 = R_3 = H$[b]	7.0	67
5	$R_2 = H$; $R_1 = R_3 = Me$[b]	5.2	126
6	$R_3 = H$; $R_1 = R_2 = Me$[a]	4.1	113
7	Morphine[c]	4.4	
8	Codeine[d]	30.7	

a) Administered as lactate in saline

b) Administered as HBr in saline

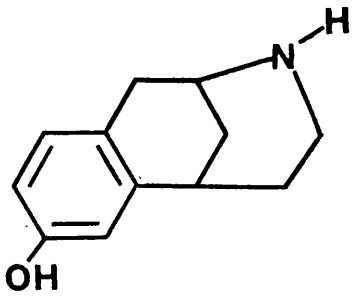
c) Administered as HCl in saline

d) Administered as phosphate in saline

2.3.3 Some structure-activity considerations of benzomorphans bearing different nitrogen substituents

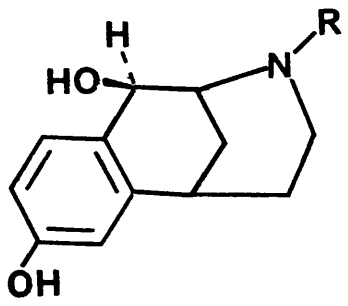
The replacement of the *N*-methyl group of 6,7-benzomorphans leads to both quantitative and qualitative changes in the structure-activity relationships. It is, however, pertinent to point out that the need for either *N*-methyl or other conventional agonist/antagonist *N*-substituents is not exactly critical for activity. Analgesic activity has been found in compounds such as (2.41) with a secondary amine (2^{o}) group, although it is more toxic than the corresponding

N-Me compound[133].



(2.*41*)

In addition, the 2° amine of the 8β-hydroxy-6,7-benzomorphan (2.*42*; R = H) has been shown to have analgesic activity about half that of codeine in the mouse hot plate test, while the corresponding *N*-methyl analogue was inactive[128].



R = H, ED_{50} = 13.7 mg/kg

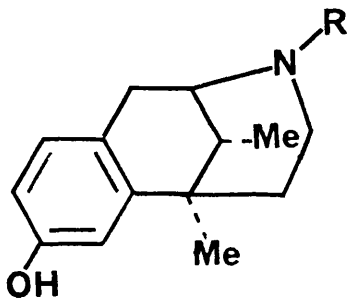
R = Me, Inactive

Codeine HCl, ED_{50} = 7.5 mg/kg

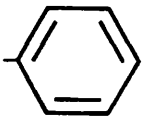
(2.*42*)

A study with a series of *cis*-*N*-alkyl-2'-hydroxy-5,9-dimethyl-2-desmethyl-6,7-benzomorphan (2.*43*) has revealed that there is a complete loss of activity when the methyl group on the nitrogen of

2'-hydroxy-5,9-dimethyl-6,7-benzomorphan (entry 1, Table 5) is replaced by ethyl, propyl or butyl, but is restored when the group on nitrogen becomes amyl[134,135]. (Table 5).



(2.*43*)

a) R = $-CH_2CH_2-$ 

(ED_{50}= 0.20 mg/kg)

b) R = $-CH_2-CH=CMe_2$

(AD_{50}=3.9 mg/kg)

c) R = $-CH_2-C-C_3H_5$

(AD_{50}=0.02 mg/kg)

However, the *N*-propyl compound (entry 3, Table 5) is one of the most potent morphine antagonists known (AD_{50} = 0.019 mg/kg, cf. Nalorphine 0.13 mg/kg)[136].

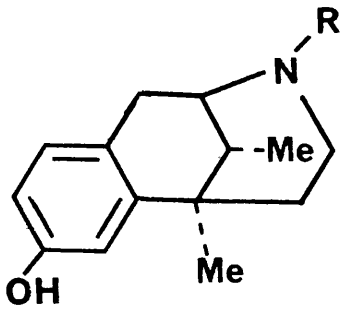
Table 5. Analgesic activity of some α-2-alkyl-2'-hydroxy-5,9-dimethyl-6,7-benzomorphans (2.*43*)[135].

Entry	R	ED_{50} (mg/kg)
1	Me	3.0
2	Et	I[a]
3	Pr	I[a]
4	Bu	I[a]
5	Am	2.1
6	Hex	1.5

a) Inactive

Replacement of the *N*-methyl of 2'-hydroxy-5,9-dimethyl-6,7-benzomorphan with an *N*-phenethyl group gave phenazocine (2.*43*a) which is a potent agonist, effective both orally and parenterally, with less abuse potential than morphine[91,137]. Similar replacement with classical antagonist substituents such as dimethylallyl and cyclopropylmethyl gave pentazocine (2.*43*b) and cyclazocine (2.*43*c) respectively. The former, though a weak antagonist, is the first narcotic antagonist analgetic to be used in man[138], and the latter is a potent narcotic antagonist and analgetic[139].

More recently, a new gradation of antagonist to agonist properties in benzomorphans has been obtained by various *N*-furylalkyl substituents[140]. The 2-arylethyl derivative 2.*44*a is a potent analgesic



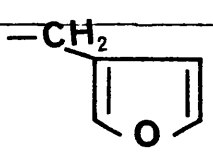
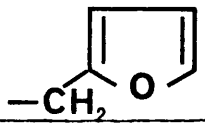
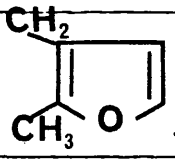
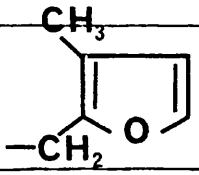
(2.*44*)

a: R = $-CH_2CH_2$-(furan-2-yl)

b: R = $-CH_2$-(furan-2-yl)

(30x morphine)[141], while the lower homologue (2.*44*b) has only feeble analgesic properties but is as potent an antagonist as nalorphine. The activity profile of (2.*44*b) may be varied by structural modifications, illustrated in Table 6.

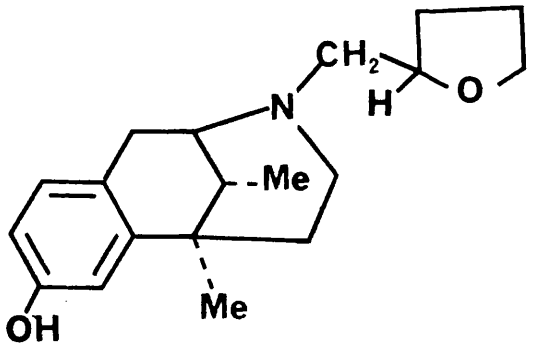
Table 6. Pharmacological properties of some *N*-furylmethyl-6,7-benzomorphan, and derivatives[140].

R in 2.46b				
Antagonism[a]	+++	+++	+	None
Analgesic[b]	none	+	++	+++

a) 50% suppression of morphine analgesic in mice by the tail clip test.

b) Tail-clip, hot plate and writhing tests in mice.

In sharp contrast, the *N*-tetrahydrofuryl benzomorphan (2.*45*), saturated analogue of (2.*44*b) is an analgesic without antagonist properties[142].

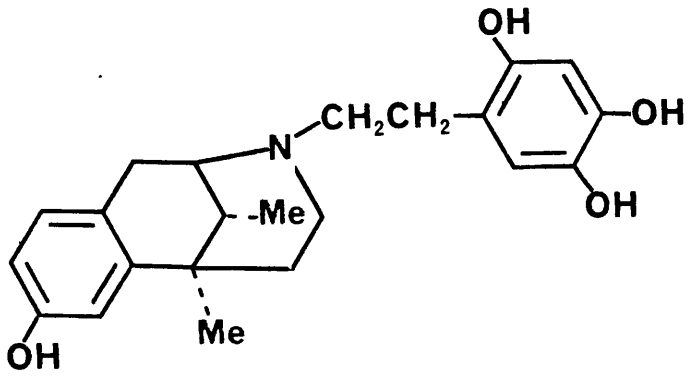


(2.*45*)

N-substituted benzomorphans as receptor probes

Several benzomorphan derivatives with specific *N*-substituents, are used as receptor probes. Examples include the *N*-2-hydroxyalkyl

and *N*-2-bromoalkyl compounds prepared by May *et al.* for their capacity to irreversibly interact with narcotic analgesic receptors. None of the compounds produced showed any marked long-lasting activity[143]. Another example is *N*-(2,4,5-trihydroxyphenylethyl)-normetazocine (2.*46*) prepared by Rice *et al.*[144] in an attempt to deliver a 6-hydroxyldopamine-like alkylating moiety to the analgesic receptor. This compound has only a weak affinity for opiate receptors (neuro-



(2.*46*)

blastoma x glioma cells).

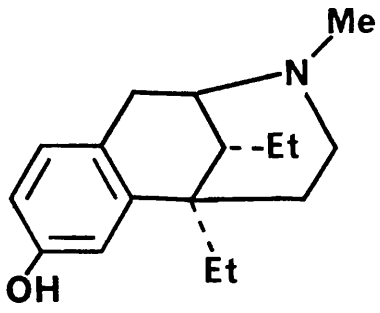
From the examples presented above, it is clear that agonist or antagonist activity is not limited to the classical *N*-substituent such as *N*-CH_3, *N*-allyl or *N*-CH_2-C-C_3H_5 or even to the tertiary amine as previously believed. It is now thought that the overall structure and geometry of a particular compound has an overriding effect concerning the ratio of agonist and antagonist activity.

2.3.4 Stereochemical Aspects

As with other classes of potent analgesics with asymmetric centres, the influence of molecular geometry on the analgesic response

of 6,7-benzomorphans has been clearly demonstrated. The effects are not only seen with enantiomeric pairs (i.e. molecules related as object to mirror image), but also with diastereoisomers (stereo-isomers with more than one asymmetric centre that are not related as object to mirror image), although the potency variations in the latter are usually less extreme than in the former. It has been shown, for example, that in a series of 5,9-dialkyl-2'-hydroxy-2-methyl-6,7-benzomorphans (Section 2.3.2), the 9β-(*trans*) isomers are always more potent than the 9α-(*cis*-) isomers. The *cis*-isomers have little or no ability to substitute for morphine in addicted monkeys, whereas the *trans*- isomer does suppress withdrawal symptoms in addicted monkeys[95].

May and Eddy, have resolved *cis*-5,9-diethyl-2'-hydroxyl-2-methyl-6,7-benzomorphan (2.47), and demonstrated a stereospecific separation between analgesic activity (as measured by the hot plate technique) and addiction liability, as assessed in the monkey[109]. The laevo-rotatory (-) isomer was as active as morphine and twice as active

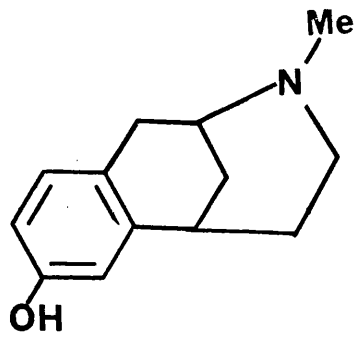


(±) (2.47)

as the racemate in the mouse hot plate. It precipitated withdrawal in addicted monkeys and displayed analgesic antagonist properties in the rat tail-flick test[145]. On the other hand, the dextrorotatory

isomer (+) had 1/10th the analgesic activity of the antipode and showed physical dependence capacity in monkeys. The low physical dependence of the racemate (2.47) is attributed to antagonism between the two antipodes because of the antagonist activity shown by the (-) isomer. This same trend was observed when 5-phenyl-9-methyl and 5-propyl-9-methylbenzomorphan derivatives were resolved and tested[146].

However, the reports that strong analgesic activity and narcotic antagonism are found in the *laevo* forms of benzomorphans and weak analgesic and physical dependence capacity in the *dextro* forms has not proved to be a general principle. For example, both optical isomers of (2.48), lacking a quaternary carbon, were analgesics with no physical dependence capacity, and both showed antagonist properties[147]. The same observation was made on the 9α and 9β-methyl isomers.



(2.48)

2.3.5 Concluding Remarks

From the structure-activity relationships treatise in the preceeding sections, the fundamental structural features associated with analgesic activity in the 6,7-benzomorphans seem to be the presence of an aromatic ring bonded to a saturated two or three carbon chain, terminating with an amino nitrogen. To be more specific, the presence of an appropriately positioned phenolic hydroxyl, tertiary amino functionality and a quaternary carbon appear to enhance analgesic activity in most cases. In addition, the delicate balance between the influence of ring substituents, *N*-substituents and stereochemical factors in determining the nature and level of activity of any particular benzomorphan has been highlighted.

2.4 Aims and Objectives of the present work

The lower analgesic agonist potency in the mouse hot-plate test of *cis*-2,3,5-trimethyl-6,7-benzomorphan when compared with that of the *trans*-2,4,5-trimethyl isomer has been attributed tentatively to the occurrence of hindrance of the nitrogen lone pair in the former, and this led to the proposal by Parfitt and Walters that hindrance of the tertiary nitrogen lone pair in morphine-like analgesics may have some bearing on both the level and type of analgesic activity exhibited. One of the aims of this thesis is to investigate further the possible non-bonding electron involvement in analgesic activity by obtaining data on:

i) 3-monosubstituted-6,7-benzomorphans

and ii) 3,3-disubstituted-6,7-benzomorphans

The main objectives were to assess the contribution of the effect on molecular geometry of the orientation of the 3-alkyl group, and also to impose conformational constraints on the nitrogen lone pair in the 3,3-disubstituted compounds in the hope that any change in activity may throw some light on its role in receptor binding.

In addition, it was considered desirable to obtain phenolic analogues of the 3- and 4-methyl-6,7-benzomorphans, since a phenolic group enhances activity in benzomorphans generally and to secure data which complements those on the 9-methyl analogues.

Finally, novel *N*-amidinobenzomorphans in the α-5,9-dimethyl derivatives were prepared. The objective here was to observe the effects on analgesic activity of

i) an increase in the basicity of the nitrogen centre

and ii) a shift of the positive charge centre from nitrogen to carbon.

The work in this thesis therefore entailed:

i) Syntheses

ii) Separation of isomers where applicable

iii) Configurational assignment

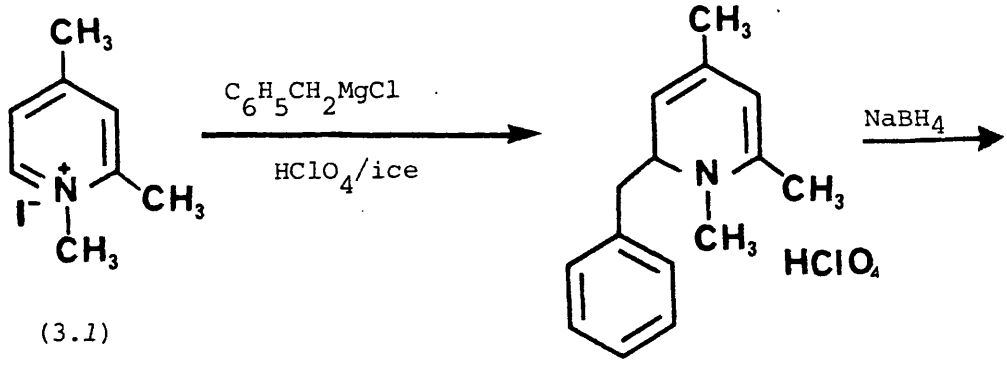
iv) Pharmacological evaluation.

PART II

DISCUSSION

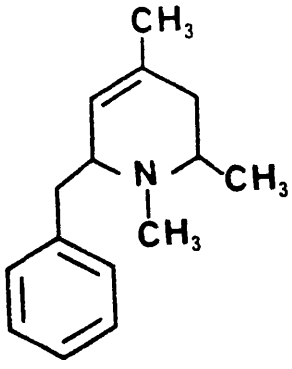
CHAPTER 3

The Syntheses and Structure-Activity Correlations of Some 6,7-Benzomorphans



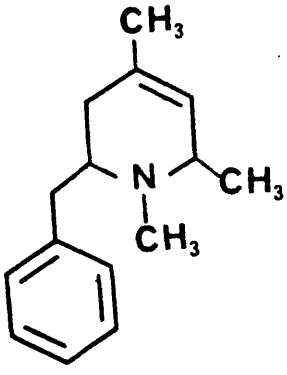
(3.1)

(3.2)



(3.3)

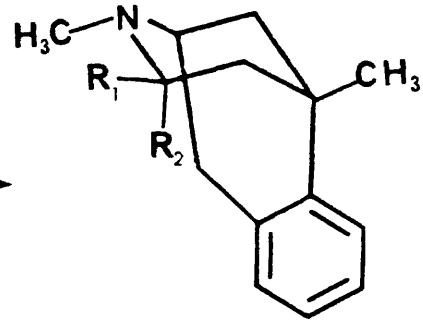
+



(3.4)

(i) 47% aq HBr

(ii) 45% HBr in HOAc



(3.5) $R_1 = CH_3$, $R_2 = H$

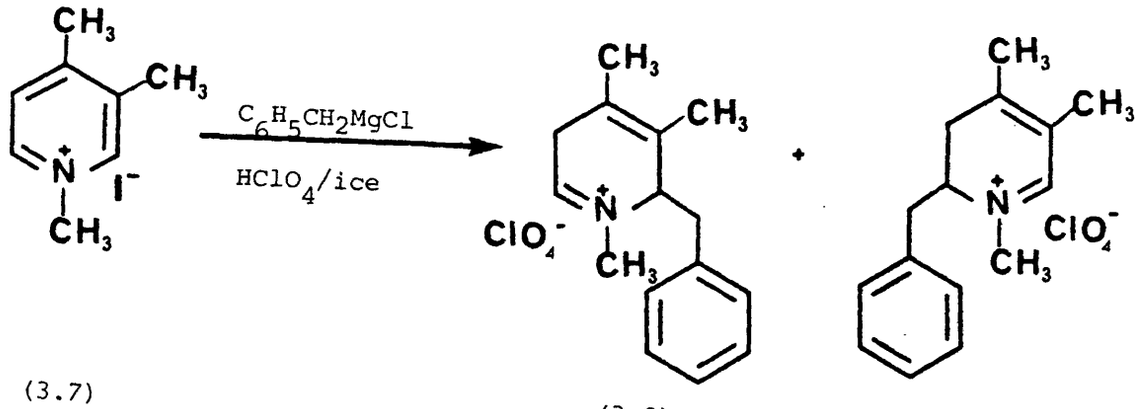
(3.6) $R_1 = H$, $R_2 = CH_3$

SCHEME 5

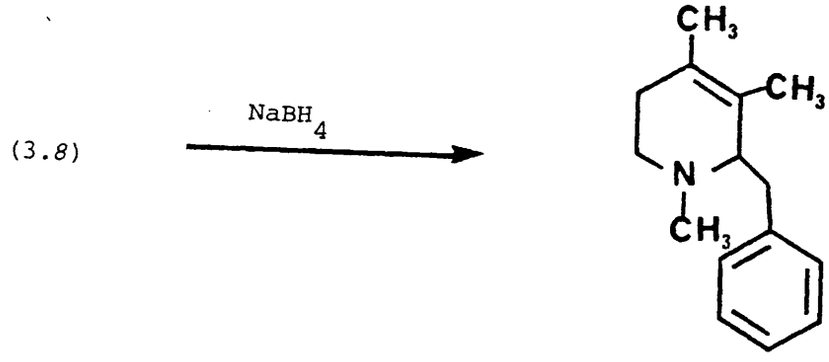
3.1 3-Substituted-6,7-benzomorphans

The syntheses of 6,7-benzomorphans for use in subsequent reactions are first discussed.

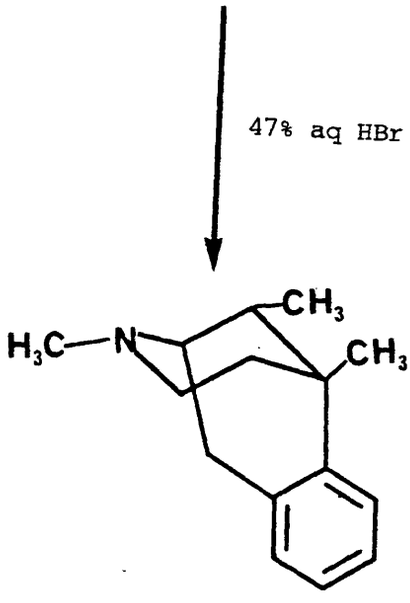
2,3,5-Trimethyl-6,7-benzomorphan was synthesized by the Grewe route as illustrated in Scheme 5. Thin layer chromatography (TLC) and proton magnetic resonance (^{1}H n.m.r.) of the crude cyclisation product showed two isomers. An earlier report by Parfitt and Walters[129] described only a single isomer. The major isomer, (±)*cis*-2,3,5-trimethyl-6,7-benzomorphan (3.5), was isolated as the hydrochloride and the minor isomer, (±)*trans* -2,3,5-trimethyl-6,7-benzomorphan (3.6), as the oxalate salt. ^{1}H N.m.r. examination of the two isomers revealed differences in both the 3-CH_3 and *N*-CH_3 chemical shifts (see Table 7). The *cis* isomer (3.5) showed a 3-CH_3 doublet resonance at δ0.92 ppm, and the *trans*-isomer a doublet at 0.44 ppm. Examination of Dreiding models and the Bovey-Johnson shielding map[148] showed that if the piperidine ring is in the more favourable chair form, the 3-CH_3 protons in the *trans*-isomer (3.6) would lie within the aromatic diamagnetic shielding zone. Hence, the high field absorption of the 3-CH_3 protons in the *trans*-isomer. The *N*-methyl proton resonance in the *cis*-isomer is slightly upfield of that in the *trans* isomer. In addition, the hydrochlorides of (3.5) and (3.6) exhibit epimerism about nitrogen, as is evident by the duplication of *N*-Me and other signals in the ^{1}H n.m.r. studies (Table 7, entries 3 and 4;p.86). Similar observations have been made for isomeric 4-phenyl-piperidines with preferred axial 4-phenyl-piperidine conformations[149,150].



(3.7) (3.8) (3.9)



(3.10)



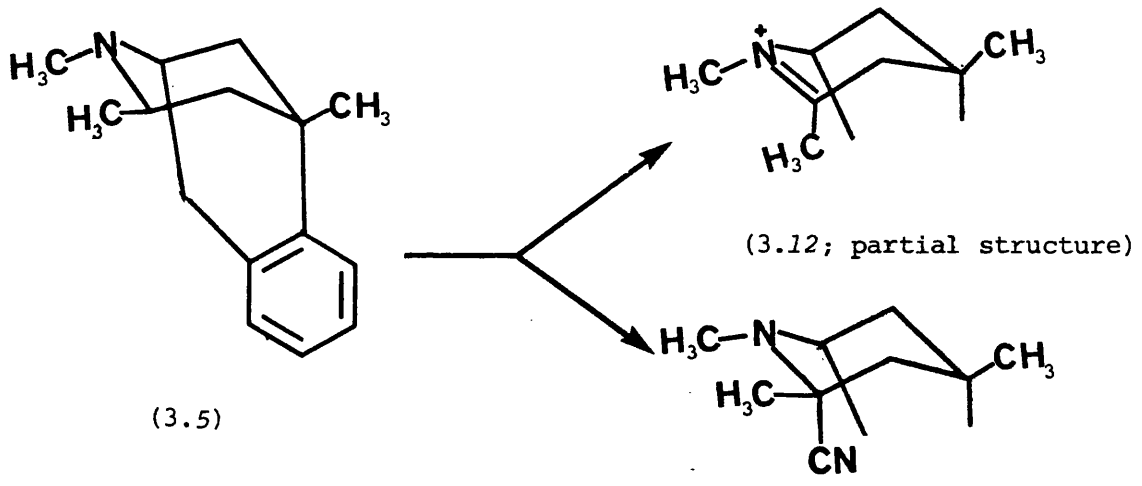
(3.11)

Scheme 6

2,5,9-Trimethyl-6,7-benzomorphan was synthesized using Fry's method[96] (see Scheme 6). The cyclised product gave exclusively α-2,5,9-trimethyl-6,7-benzomorphan (3.*11*), as deduced from inspection of the base ^{1}H n.m.r. spectrum. This spectrum showed a C-9 methyl doublet resonance at δ0.83 ppm (J = 6 Hz) and no resonance at 1.24 ppm due to the β-isomer.[151]

3.1.1 3-Substituted-2,3,5-trimethyl-6,7-benzomorphans

The difficulties in obtaining the required alkyl pyridine starting materials precluded the use of the Grewe synthesis for this series of compounds. Therefore, other possible methods of introducing a carbon-carbon bond (C-C) at the 3-position of 2,3,5-trimethyl-6,7-benzomorphan were considered. The functionalisation of the 3-position of (3.*5*) in advance by converting (3.*5*) to intermediates such as the cyclic iminium ion (3.*12*), or the 3-cyanoamine (3.*13*) appeared to offer a route to the required compounds.

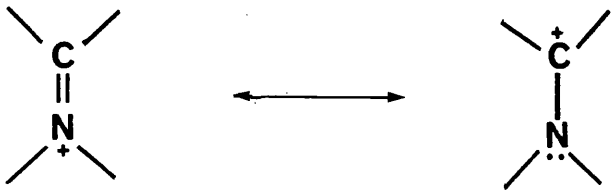


(3.*5*)

(3.*12*; partial structure)

(3.*13* , partial structure)

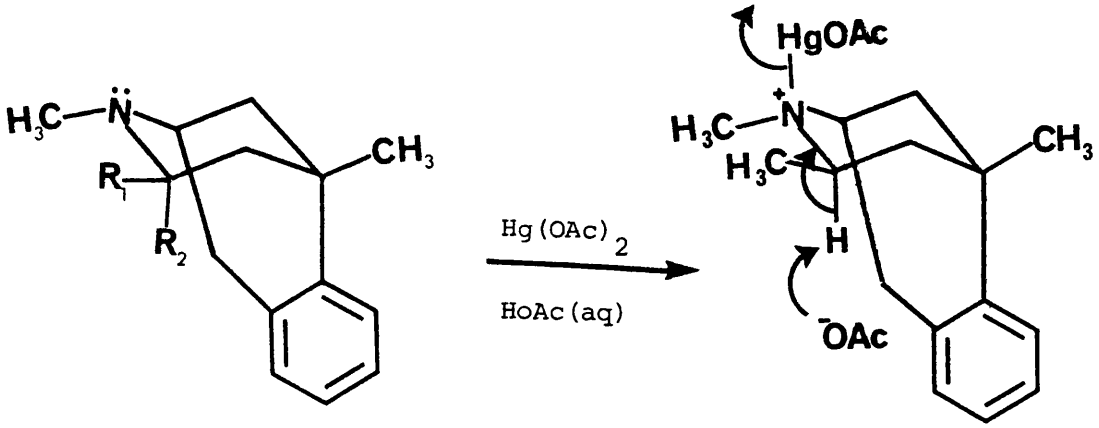
Use was made of the fact that iminium ions show properties similar to carbonyl compounds and can be thought of as a resonance hybrid of two similar charged forms (3.*14* and 3.*15*). They therefore function



(3.*14*) (3.*15*)

as electrophiles, adding nucelophiles such as cyanide ion, lithium alkyls, hydrides and Grignard reagents to form substituted amines. Iminium ions are readily available from C-protonation of the corresponding enamines,which are obtained by the oxidation of amines by various reagents, particularly mercury (II) acetate. Oxidation of cyclic amines with mercury (II) acetate gives the corresponding enamines[152]. This reaction has been applied to pethidine[153], oripavines[154] and certain alkaloids[155,156] but failed with morphine and codeine.[154] Other oxidative methods utilising benzoyl peroxide[157], manganese dioxide[158] and electrochemical methods[159] have been reported.

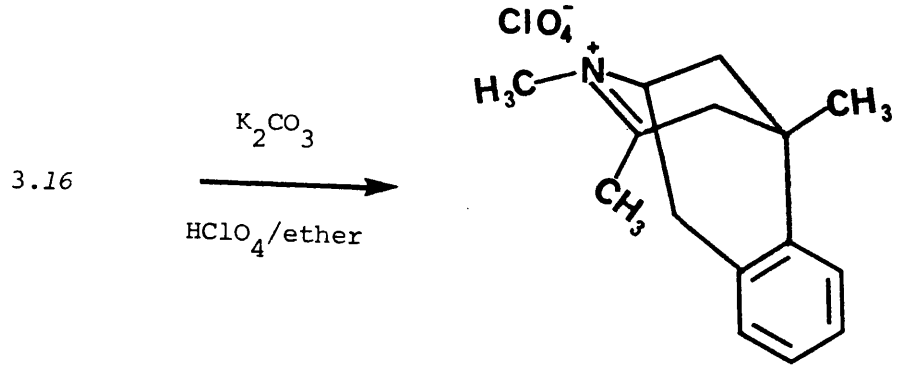
Mercury (II) acetate oxidation of both isomers of 2,3,5-trimethyl-6,7-benzomorphan (3.*5* and 3.*6*) gave $\Delta^{3,4}$dehydro-2,3,5-trimethyl-6,7-benzomorphan, isolated as the iminium perchlorate (3.*17*). The proposed mechanism[152,160] for mercury (II) acetate oxidation requires the formation of an intermediate mercurated complex (3.*16*) with nitrogen lone pair, followed by a concerted *trans*-coplanar elimination of an



(3.5) $R_1 = CH_3$, $R_2 = H$

(3.6) $R_1 = H$, $R_2 = CH_3$

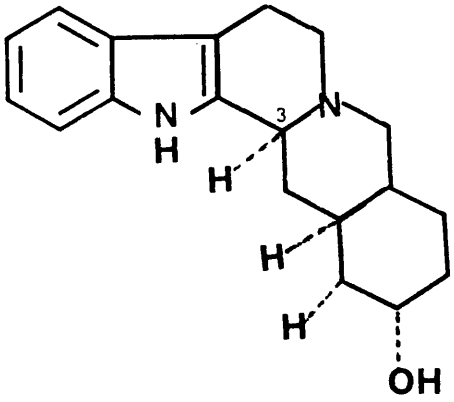
(3.16)

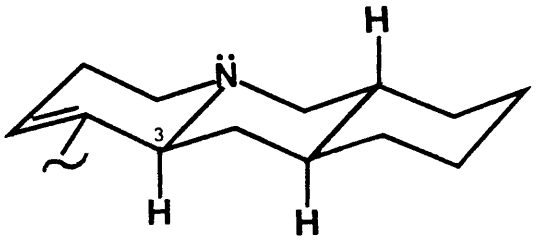


(3.17)

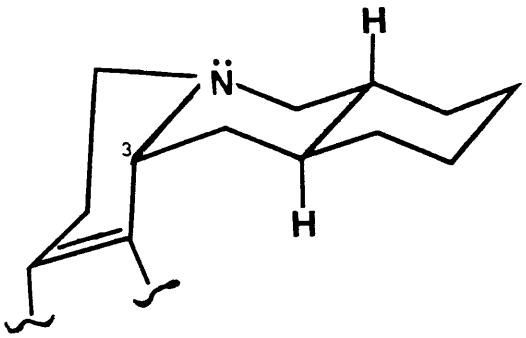
α-hydrogen and cleavage of the mercury-nitrogen bond. This four-centre elimination implies that the hydrogen to be eliminated should have a *trans*- relationship with the lone pair of electrons on nitrogen, or be capable of attaining *trans*-coplanarity with the *N*-Hg bond in the mercurated complex (if not sterically hindered). Indications that a *trans*-coplanar relation was necessary are found

in the result of studies of mercury (II) acetate oxidation of alkaloids. For example, yohimbine (3.*18*) is readily oxidised at C-3 by mercury (II) acetate whereas pseudoyohimbine (3.*19*) is unreactive[161].





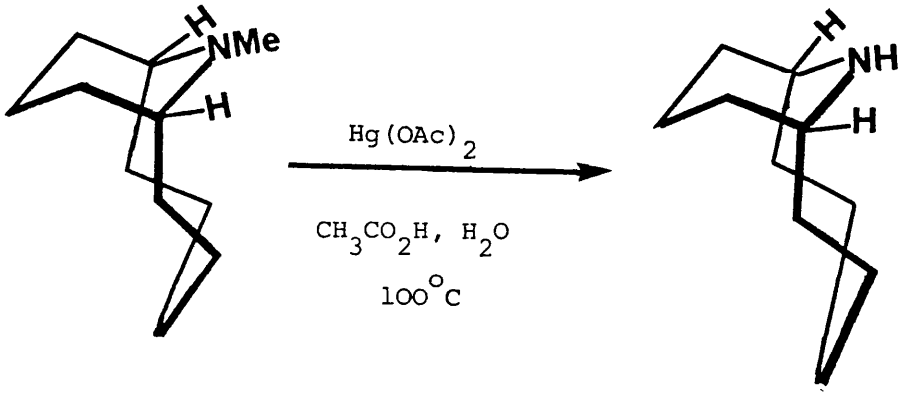
(3.*18*, partial formula)



(3.*19*, partial formula)

Additional evidence is provided by the mercury (II) acetate oxidation of 11-methyl-11-azabicyclo (5,3,1) hendecane (3.*20*), a tertiary amine where the hydrogens on the equivalent α-*tert* carbons are sterically prevented from attaining *trans*-coplanarity with *N*-Hg bond in the mercurated complex. The product is the *N*-demethylated

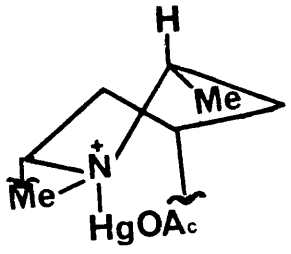
analogue (3.*21*) resulting from abstraction of one of the protons of the *N*-methyl group which has virtually unrestricted rotation and can be aligned readily in the steric relationship favourable for oxidation[160].



(3.*20*) (3.*21*)

From the above requirements, and assuming a chair conformation of the piperidine ring of 2,3,5-trimethyl-6,7-benzomorphan, the formation of the iminium salt (3.*17*) from the *trans*-isomer (3.*6*) seems anomalous as it apparently does not possess any α-hydrogen *trans*- to the nitrogen lone pair, except those in the *N*-methyl group. The absence of any *N*-demethylated material in the product excludes the elimination of one of the *N*-methyl protons and the loss of the other proton at C-1 would contravene Bredt's rule. However, the ability of (3.*6*) to form salts epimeric about nitrogen (see p.63) together with the apparent lack of conformational preference of reactive mercury species, for example HgBr[162] and HgCl[163], makes the formation of *N*-mercuriacetate epimeric about nitrogen a possibility. Inspection of a model of (3.*6*) revealed that the equatorial proton at C-3 is capable of *trans*-coplanarity with an equatorial

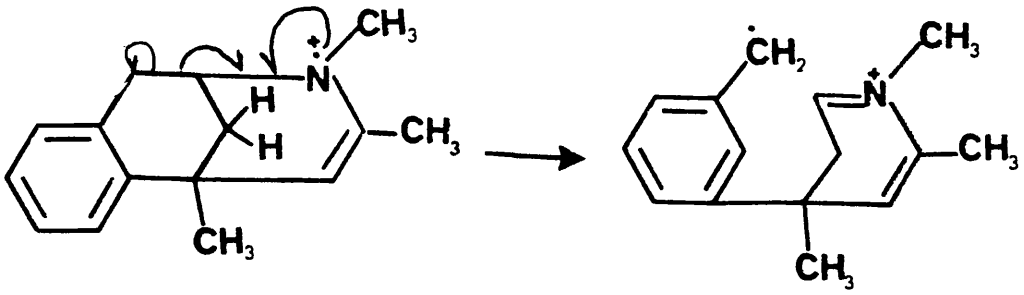
N-Hg bond in a twist conformation of the piperidine ring. Therefore, *trans*- coplanar elimination of this proton could lead to the same



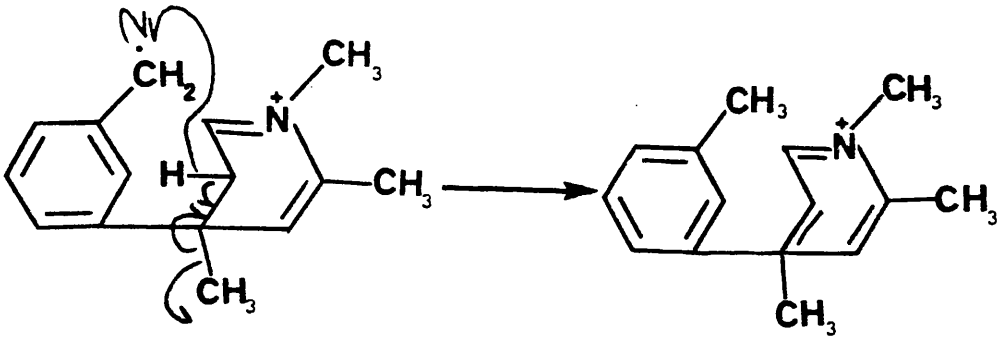
(3.*16*, partial formula)

iminium salt (3.*17*) as the one obtained from the *cis*-isomer and, consequently, may explain this anomaly. It is pertinent, however, to point out that there are different schools of thought on the conformational preference of the acetoxymercuric group (HgOAc), for example, on cyclohexane. Previous work by Jensen *et al.*[164] concluded that the acetoxymercuri group has no conformational preference but, more recently, Anet and Krane[163], using high field (59 Kgauss) ^{1}H and ^{13}C n.m.r., have reported that the HgOAc group exists preferentially in the axial form on cyclohexane. Given close parallels in conformation cyclohexane and piperidine rings, our work seems to agree with the findings of Jensen *et al.*

The structure of the iminium salt (3.*17*) was confirmed by the carbon-13 nuclear magnetic resonance (^{13}C n.m.r.) chemical shift of the C-3 carbon at δ188.09 ppm (Table 11, p. 110) and a corresponding $\diagdown C = \overset{+}{N} \diagup$ band at 1680 cm^{-1} in the infra-red (i.r.) spectrum, together with downfield shifts of the 2-, 3- and 5-methyl

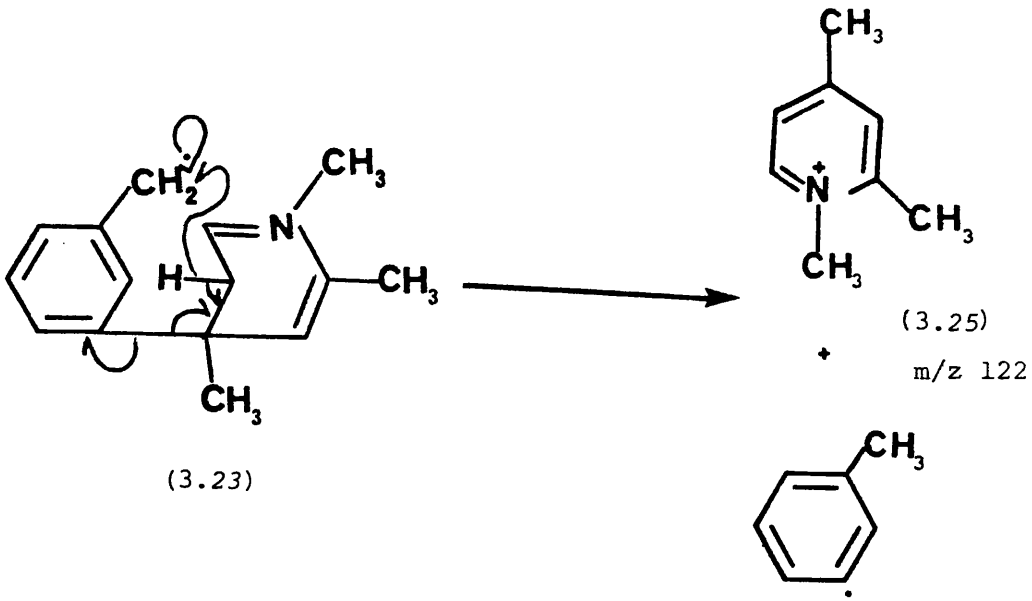


(3.22) (3.23)



(3.23) (3.24) + $CH_3^{\cdot}$

m/z 198.05



(3.23) (3.25) + m/z 122

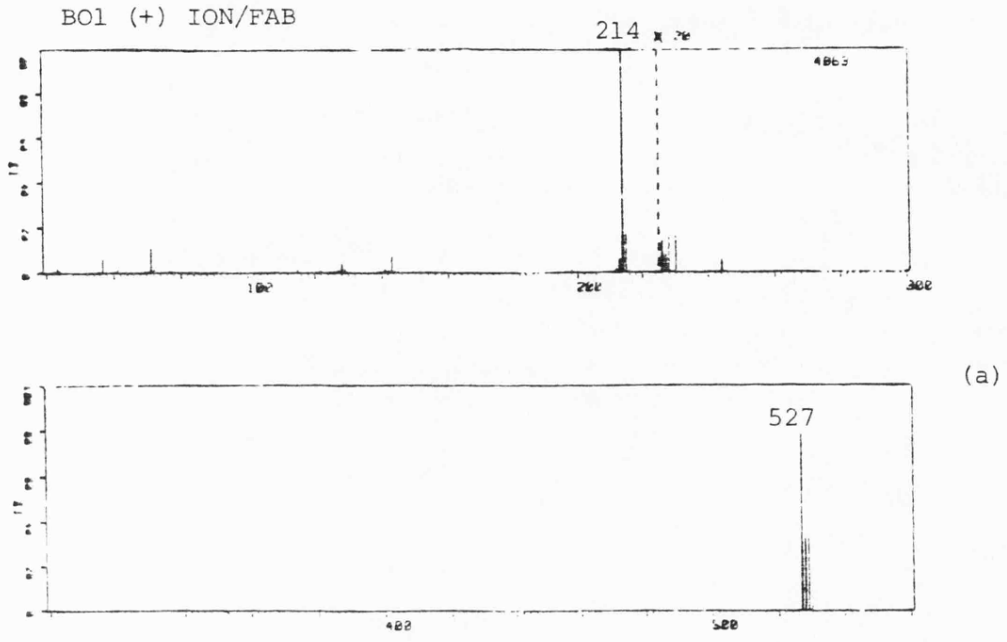
Scheme 7

^{1}H n.m.r. resonance relative to corresponding values in 3.5 (Table 7). Positive ion fast atom bombardment mass spectroscopy (+ve ion FAB) gave the $(M+1)^+$ parent ion at m/z 214.06 (100%) (Fig. 1) and electron impact (EI) mass spectrometry gave the M^+ due to the enamine (3.22) at m/z 213.12 (34.13%). Other diagnostic peaks (EI) are at m/z 198.05 (19.4%), due to loss of the C-5 angular methyl group, and 122.03 (27.8%) due to the loss of the 1,2,4-trimethyl pyridinium ion (Scheme 7). The base peak was observed at m/z 71.

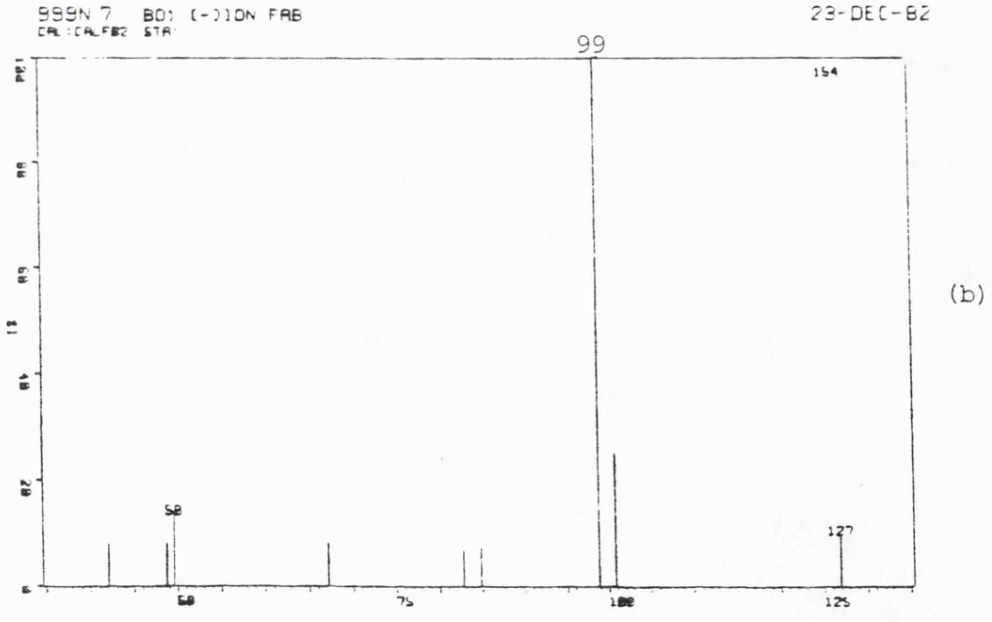
3-Cyano-2,3,5-trimethyl-6,7-benzomorphans

An earlier method[152,174] of α-cyanation of tertiary amines involves the aqueous cyanide treatment of the iminium salt from mercury (II) acetate oxidation. More recently, Portoghese[165] described a mild method of α-cyanation in good yields, of a series of compounds related to morphine. The process involves the oxidation of the amine with hydrogen peroxide, esterification of the resultant *N*-oxide with trifluoroacetic anhydride and subsequent treatment with aqueous potassium cyanide. Both methods are employed in the present work.

Aqueous potassium cyanide treatment of the iminium salt (3.17) afforded 3-cyano-2,3,5-trimethyl-6,7-benzomorphan (3.26). The structure of the 3-cyanoamine (3.26) was confirmed by -C≡N i.r. absorption at 2225 cm^{-1} and the corresponding ^{13}C n.m.r. shift at δ119.5 ppm. In the ^{1}H n.m.r. spectrum, the 3-CH_3 protons resonated downfield at 1.37 ppm as the expected singlet, compared to the 3-CH_3 protons of the unsubstituted base (entries 1 and 6, Table 7). The configuration of the 3-cyano group was assigned as axial from a



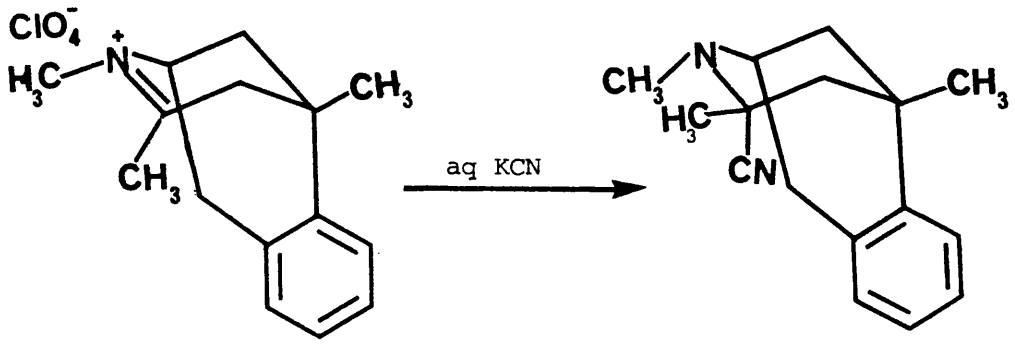
(a)



(b)

Figure 1. FAB mass spectrum of iminium perchlorate (3.17):

(a) positive ion; (b) negative ions

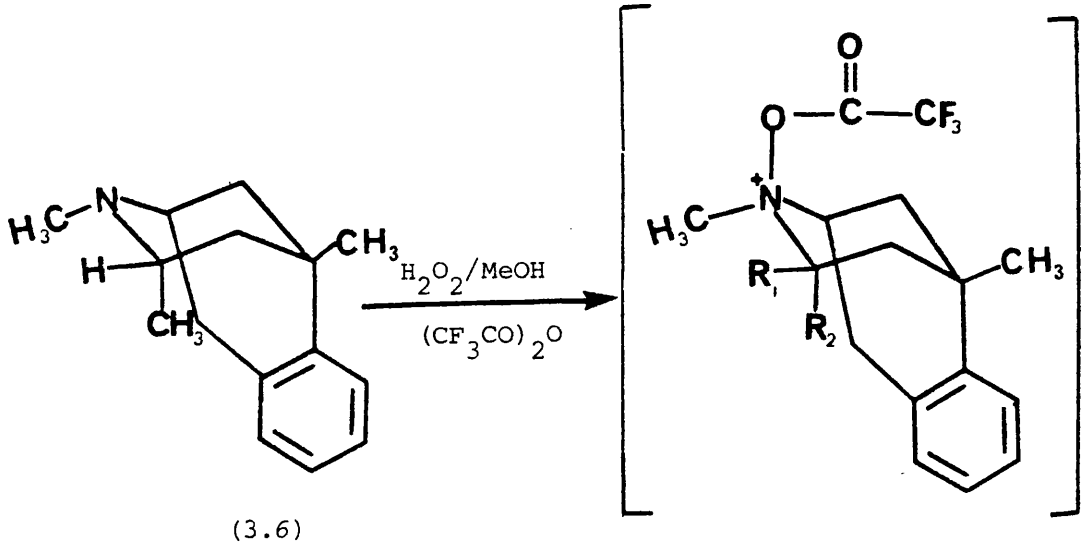


(3.17) (3.26)

consideration of other ^{1}H and ^{13}C n.m.r. data.

Lithium aluminium hydride reduction of (3.26) gave a 50:50 mixture of *cis* and *trans* -2,3,5-trimethyl-6,7-benzomorphan. In this reaction, lithium aluminium hydride substitutes at C-3 rather than reduce the nitrile group, and the reaction would be SN_1 judging from the formation of an almost equal mixture of isomers from a single 3-cyano isomer. Similar reactions have been reported previously[152,174].

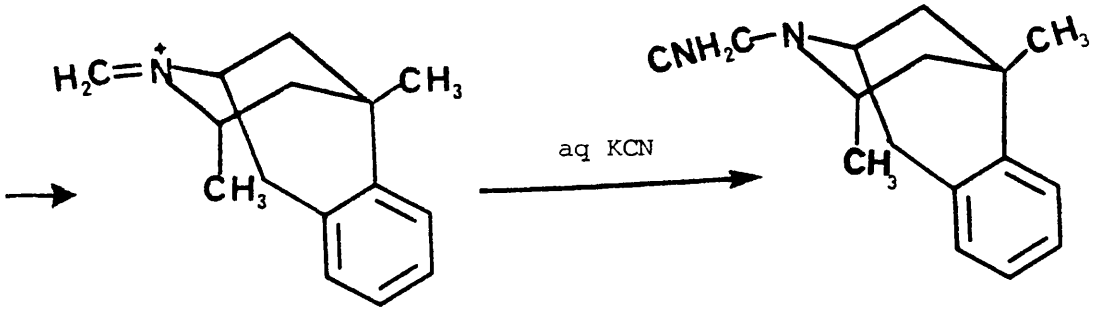
When Portoghese's method[165] (a modified Polonovski reaction) was employed, α-cyanation of (3.5) proceeded readily to afford the expected 3-cyano-3-methyl-6,7-benzomorphan (3.26) in 67% yield, identical to the mercury (II) acetate/potassium cyanide product. However, the axial C-3 methyl substrate (3.6) gave 2-cyanomethyl-3,5-dimethyl-6,7-benzomorphan (3.29) in 60% yield (see Scheme 8). This seems anomalous considering that the two isomers gave the same product in the mercuric acetate oxidation. During the Portoghese approach, intermediates were not isolated and the reaction is believed



(3.6)

(3.27)

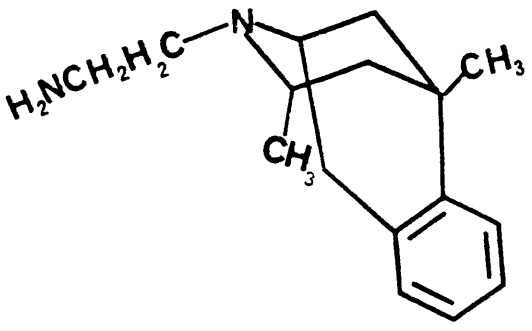
R_1 = H, R_2 = CH_3



(3.28)

(3.29)

3.29 $\xrightarrow{LiAlH_4}$

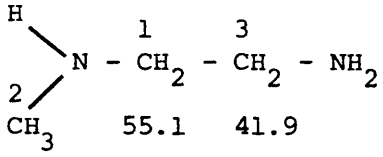


(3.30)

SCHEME 8

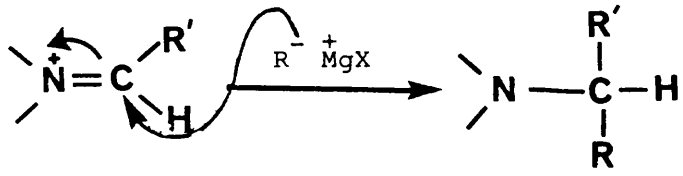
to involve a β-*trans*-elimination of the trifluoroacetoxyammonium ester (3.*27*) to afford, normally, the endocyclic iminium salt (3.5 → [3.*27*, $R_1 = CH_3$] ⟶ 3.*17*). The stereochemistry of 1-alkyl-piperidine quaternisations[166,167] and *N*-oxidation[168,169] has been demonstrated to occur largely from equatorial *N*-alkyl conformers where the entering group is preferentially axial and this is likely to be the case with 2-methyl benzomorphans. However, where the 3-methyl group is axial, the trifluoroacetate ester cannot give an endocyclic iminium salt *via* a *trans*-β-elimination, because the hydrogen at the 3-position is not *trans*-coplanar to the trifluoroacetoxy group on nitrogen. Elimination occurs from the *N*-CH_3 group to afford an intermediate exocyclic iminium salt (3.*28*) to which CN^- adds readily. The 2-cyanomethyl-3,5-dimethyl-benzomorphan (3.*29*) was characterised from its ^1H and ^{13}C n.m.r. data. The ^1H n.m.r. spectrum showed a distinct downfield shift of the 2-position methylene group, appearing as a 2H singlet at δ3.48, with the corresponding ^{13}C signal observed at δ36.41 ppm. (entry 20, Table 11). The appearance of the 3-CH_3 group as a doublet distinguishes (3.*29*) from the 3-cyano-2,3,5-trimethyl-6,7-benzomorphan (3.*26*) where the 3-CH_3 appeared as a singlet (compare entries 6 and 7, Table 7).

Lithium aluminium hydride reduction of (3.*29*) to the ethylenediamine derivative (3.*30*), which was isolated as its oxalate salt, added support to the structural assignment. The ethylenediamine methylene groups of (3.*30*) appeared as an apparent 4H singlet at δ2.76 ppm in the ^1H n.m.r. spectrum (Table 7, entry 8) with the corresponding ^{13}C shifts at δ54.34 and 39.82 ppm, data comparable to analogous shifts of C-1 and C-3 of *N*-methylethylenediamine[170,171].



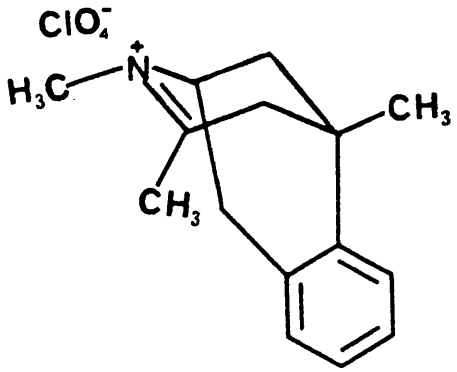
3-Alkyl-2,3,5-trimethyl-6,7-benzomorphans

Simple iminium salts have been shown to react with organometallic reagents to give C-alkylated derivatives, and various Grignard reagents have been employed[172,173] (see Scheme 9 for general reaction)



SCHEME 9

The introduction of a second alkyl group at the 3-position of 2,3,5-trimethyl-6,7-benzomorphan was achieved by reacting the cyclic iminium salt (3.17) with methyl, benzyl and allyl-magnesium halides (Scheme 10). Both allyl and benzyl magnesium halides gave the expected C-3 alkylated products while no alkylated product could be isolated with the methyl Grignard. A similar trend was observed during the reaction of methyl and benzyl magnesium halides with $\Delta^{1,(2)}$-1,2,6-trimethyl piperidinium perchlorate, when the yield from the former was very poor[174]. The greater reactivity of the benzyl and allyl Grignards can be attributed to the greater stability of the carbanion formed from them, due to resonance.



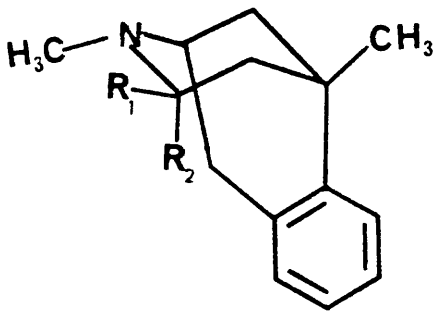
(3.17)

CH_3MgI

$C_6H_5CH_2MgCl$ and

$CH_2=CH-CH_2MgBr$

MIXTURE OF PRODUCTS



(3.31) $R_1 = CH_3$, $R_2 = -CH_2Ph$

(3.32) $R_1 = -CH_2-Ph$, $R_2 = CH_3$

(3.33) $R_1 = CH_3$, $R_2 = -CH_2-CH=CH_2$

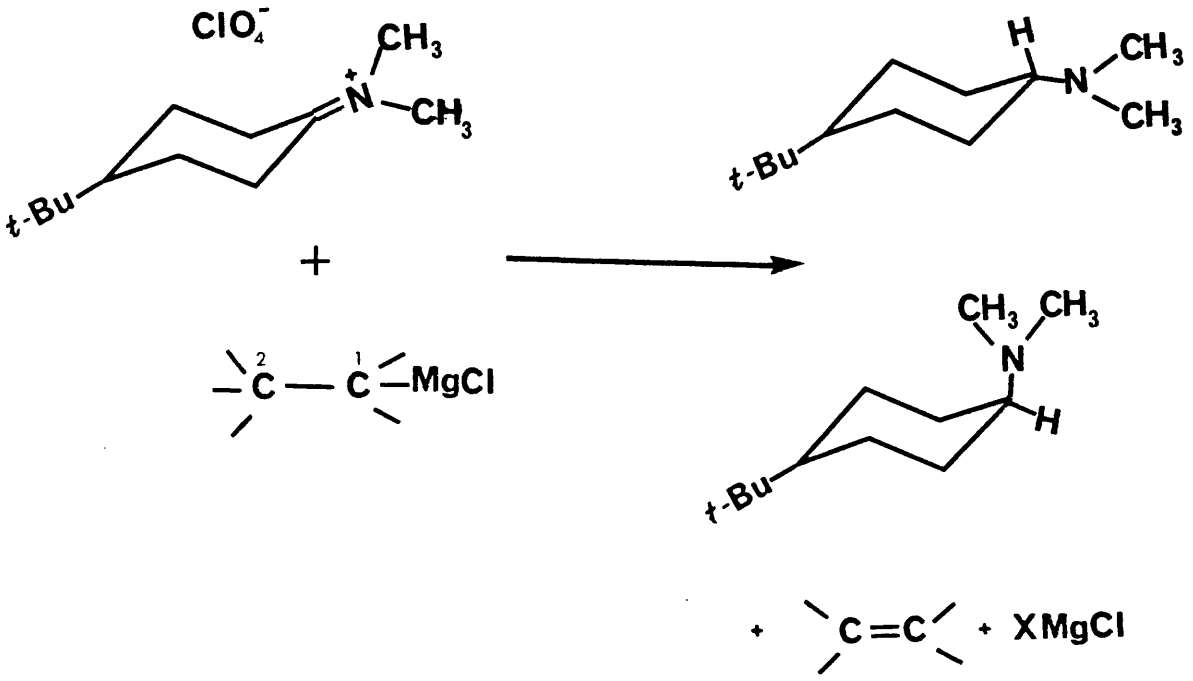
(3.34) $R_1 = -CH_2CH=CH_2$, $R_2 = CH_3$

SCHEME 10

The product from the reaction of (3.*17*) with methylmagnesium iodide (Scheme 10) was an oil which darkened on exposure to air. ^{1}H N.m.r. analysis of the crude product revealed a pair of doublets at δ0.40 and 0.90 ppm attributable to both *cis* and *trans*-2,3,5-trimethyl-6,7-benzomorphan, and additional resonances indicated further components. The observed colour change could be due to the presence of enamine which would display instability to air. Any such enamine present could arise from basification of any unreacted iminium salt during the work up procedure. The appearance of signals due to *cis* and *trans*-2,3,5-trimethyl-6,7-benzomorphan (3.*5* and 3.*6*) implies that methylmagnesium iodide has caused some reduction of the iminium salt to the saturated amine. Although similar observation have been made in the reaction of *tert.*-butyl-4-*N*,*N*-dimethylcyclohexyl iminium perchlorate with a Grignard reagent having a hydrogen atom on carbon 2 (Scheme 11)[175], it is unclear how methylmagnesium iodide, lacking such structural property, could effect such a reduction.

3-Benzyl-2,3,5-trimethyl-6,7-benzomorphan

Benzyl magnesium chloride reacted readily with (3.*17*) to produce the two possible isomers of 3-benzyl-2,3,5-trimethyl-6,7-benzomorphan. Evidence for this came from TLC and ^{1}H n.m.r. analysis of the crude product. The major isomer (3.*32*) was separated by passage through a chromatographic column of silica gel, but attempts to obtain the minor isomer (3.*31*) were unsuccessful. The major isomer (3.*32*) was shown to have a *trans*-3-Me/5-Me configuration, on the basis of its 3-methyl proton shift (near δ0.38 ppm (s)) which implies an axial orientation and, consequently, diamagnetic shielding from



SCHEME 11

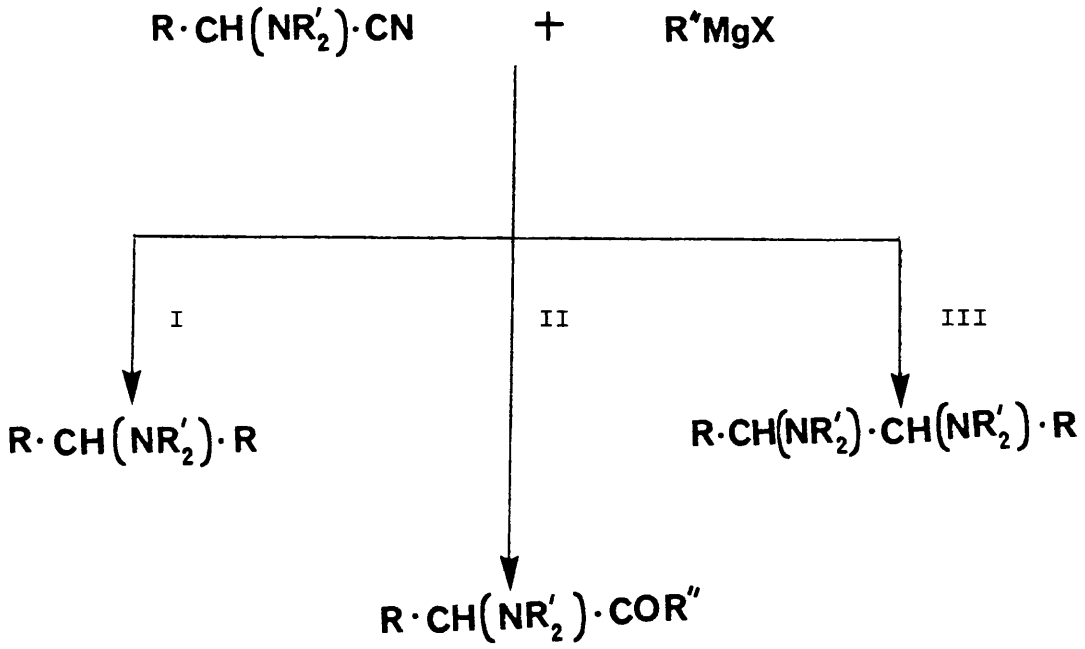
the aromatic ring of the benzomorphan nucleus. ^{13}C N.m.r. analysis was consistent with the structure and further evidence for the assignment is discussed in Chapter 4 (p. 127).

3-Allyl-2,3,5-trimethyl-6,7-benzomorphan

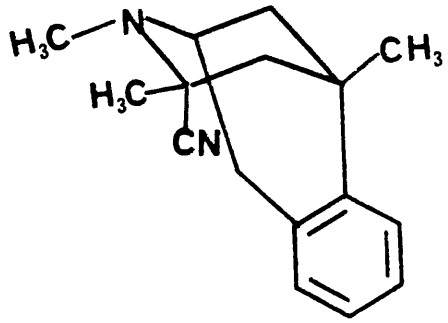
The two possible isomers of 3-allyl-2,3,5- trimethyl-6,7-benzomorphan were obtained, evidence being secured from TLC and ^{1}H n.m.r. analysis of the crude base. The isomers were separated by column chromatography on silica. The major isomer (3.*33*) has a *cis* 3-Me/5-Me configuration, while the minor isomer (3.*34*) has a *trans* 3-Me/5-Me configuration (see Chapter 4, p. 127). The axial orientation of the

3-allyl group in (3.*33*) is substantiated by the vinylic chemical shifts which are to higher field than those of (3.*34*) due to aromatic shielding (footnotes e and f, Table 7).

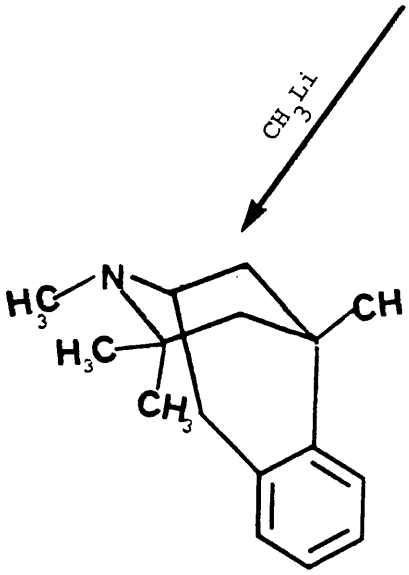
The displacement of the cyano group of an α-aminonitrile, for example, (3.*26*), by Grignard reagent or lithium alkyls also offer a route to C-3 disubstituted compounds. Although an α-aminonitrile and a Grignard reagent may interact in one of 3 ways (see Scheme 12), α-aminonitriles derived from piperidine undergo nitrile displacement (I) readily[176]. Indeed, precedents abound for the replacement of α-cyano groups in such an environment by alkyl groups of the Grignard or alkyllithium type[174,177].



SCHEME 12

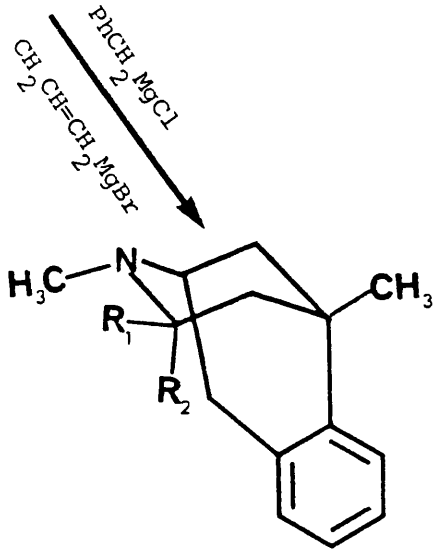


(3.*26*)



(3.*35*)

(10% yield)



(3.*31*) $R_1 = CH_3$, $R_2 = -CH_2Ph$

(3.*32*) $R_1 = -CH_2Ph$, $R_2 = CH_3$

(3.*33*) $R_1 = CH_3$, $R_2 = -CH_2CH=CH_2$

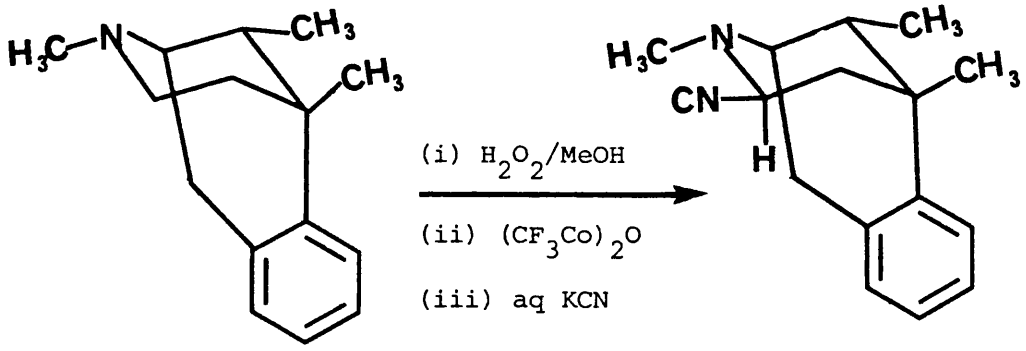
(3.*34*) $R_1 = -CH_2-CH=CH_2$, $R_2 = CH_3$

SCHEME 13

The reaction of (3.*26*) with methyllithium gave a mixture of about 10% 2,3,3,5-tetramethyl-6,7-benzomorphan (3.*35*) and 90% of (3.*26*), under all attempted conditions (Scheme 13). It proved impossible to isolate (3.*35*) in pure form. ^{1}H N.m.r. analysis of the crude product, however, showed singlets due to the C-3 methyl groups at δ0.32 and 1.05 ppm. The products from the reaction with benzyl and allyl magnesium halides (Scheme 13) show the same spectral characteristics as those from the reaction with iminium perchlorate.

3.1.2 3-Substituted-2,5,9-trimethyl-6,7-benzomorphan

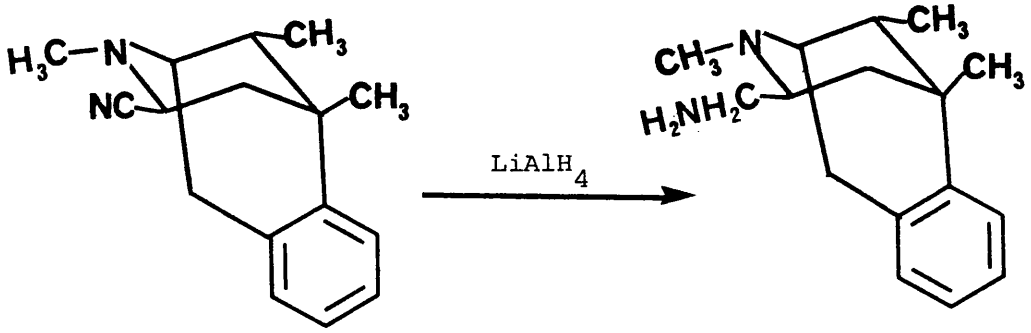
α-Cyanation of 2,5,9-trimethyl-6,7-benzomorphan (3.*11*) using Portoghese's method afforded 3-cyano-2,5,9-trimethyl-6,7-benzomorphan (3.*36*)



(3.*11*) (3.*36*)

The i.r. spectrum of (3.*36*) showed the expected -C≡N band at 2220 cm^{-1} and the corresponding carbon shift (^{13}C n.m.r.) at 119.62 ppm. ^{1}H N.m.r. (100 and 220 mHz), ^{13}C n.m.r., and lanthanide shift reagent studies showed the orientation of the 3-cyano group to be equatorial in the major product. Full evidence for this assignment will be discussed in Chapter 4 (see p. 118). The

lithium aluminium hydride reduction product of 3-cyano-2,5,9-trimethyl-6,7-benzomorphan, the 3-methylamino analogue (3.37), added support to the structural assignment.



(3.36) (3.37)

The reaction of 3-cyano-2,5,9-trimethyl-6,7-benzomorphan (3.36) with methyl, ethyl, benzyl and phenethyl magnesium halides afforded the axial 3-alkyl derivatives as the major products (Scheme 14), although traces of the minor (equatorial alkyl) isomer were always detected in the crude product. The full ^{1}H and ^{13}C n.m.r. evidence to support these assignments will be discussed in Chapter 4 (see p. 118). Attempts to obtain the 3-allyl-2,5,9-trimethyl-6,7-benzomorphan were unsuccessful.

Footnotes to Table 7

a. values in ppm from TMS

b. DMSO as solvent, TMS as standard

c. The *N*-methylene group resonates at δ3,48 ppm, as a singlet

d. Both ethylenediamine methylene protons resonate at δ2.76 ppm, as a singlet

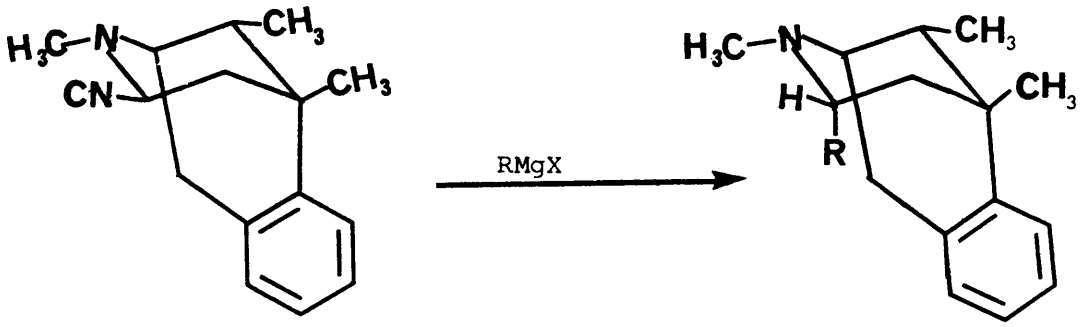
e. 3-Allyl resonances (ppm): -C*H*=CH_2- multiplet at 5.20, and the vinylic methylene at 4.06 and 4.64.

f. 3-Allyl resonances (ppm): -C*H*=CH_2- multiplet at 5.80, and the vinylic methylene at 5.04(s) and 4.90.

g. C-3 methyl (from ethyl) resonance centred on 0.44 ppm (t)

Table 7. ^{1}H chemical shifts of some 6,7-benzomorphan derivatives in $CDCl_3$[a]

Entries	Compound	N-Me	3-Me	5-Me	9-Me
1	3.5	2.40	0.90(d) (J=6Hz)	1.36	-
2	3.6	2.43	0.42(d) (J=6Hz)	1.32	-
3	3.5 HCl[b]	2.84	1.02,1.20 (d)	1.44	-
4	3.6 HCl[b]	2.74,3.02(d)	0.52,0.88 (J=7Hz)	1.32,1.44	-
5	3.17	3.65	2.34(s)	1.52	-
6	3.26	2.52	1.37(s)	1.32	-
7	3.29	c	0.69(d) (J=7Hz)	1.32	-
8	3.30	d	0.34(d)	1.32	-
9	3.32	2.56	0.38(s)	1.24	-
10	3.33 [e]	2.48	1.06(s)	1.32	-
11	3.34[f]	2.38	0.31(s)	1.32	-
12	3.11	2.40	-	1.36	0.83 (J=6Hz)
13	3.36	2.58	-	1.38	0.84
14	3.37	2.3	-	1.36	0.83
15	3.38	2.49	0.42	1.32	0.84
16	3.39	2.50	g	1.29	0.80
17	3.40	2.64	-	1.23	0.81
18	3.41	2.50	-	1.35	0.84



(3.*36*)

(3.*38*) R = CH_3

(3.*39*) R = CH_2CH_3

(3.*40*) R = CH_2 -Ph

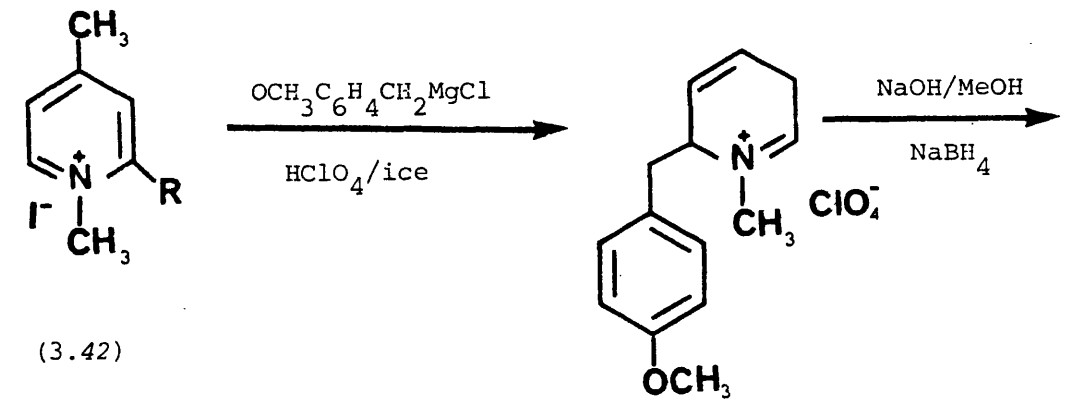
(3.*41*) R = CH_2CH_2Ph

SCHEME 14

3.2 2'-Hydroxy-6,7-Benzomorphans

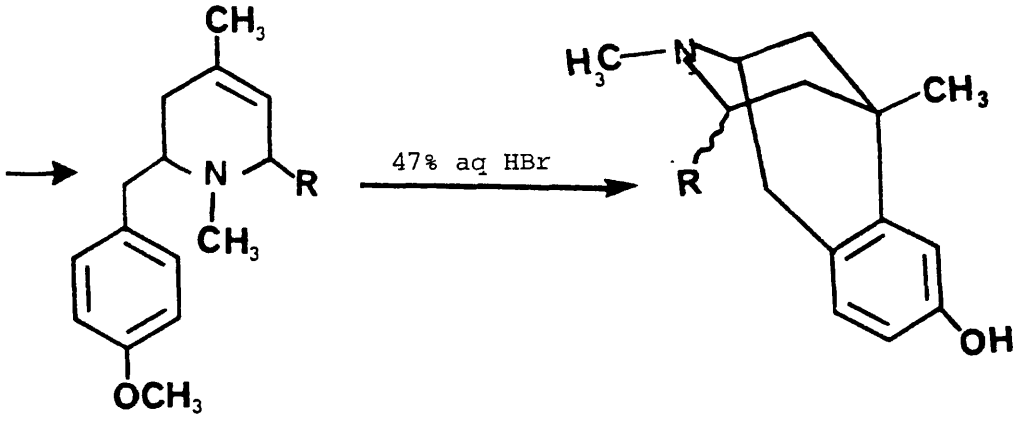
2'-Hydroxy-2,5,dimethyl-6,7-benzomorphan (3.*45*) was synthesised by the Grewe route as described by May and Murphy (Scheme 15). The structure was established by ^{1}H and ^{13}C n.m.r. studies and comparison of physical constants with literature values[15].

2'-Hydroxy-2,3,5-trimethyl-6,7-benzomorphan (3.*46*) was similarly prepared by the Grewe route as in Scheme 15 (R = CH_3). The ^{1}H n.m.r spectrum of the crude product revealed the presence of both possible



(3.42)

(3.43)



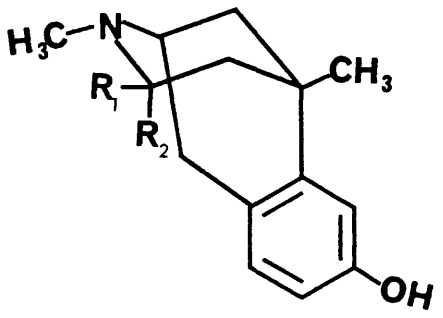
(3.44)

(3.45) R = H

(3.46) R = $-CH_3$

SCHEME 15

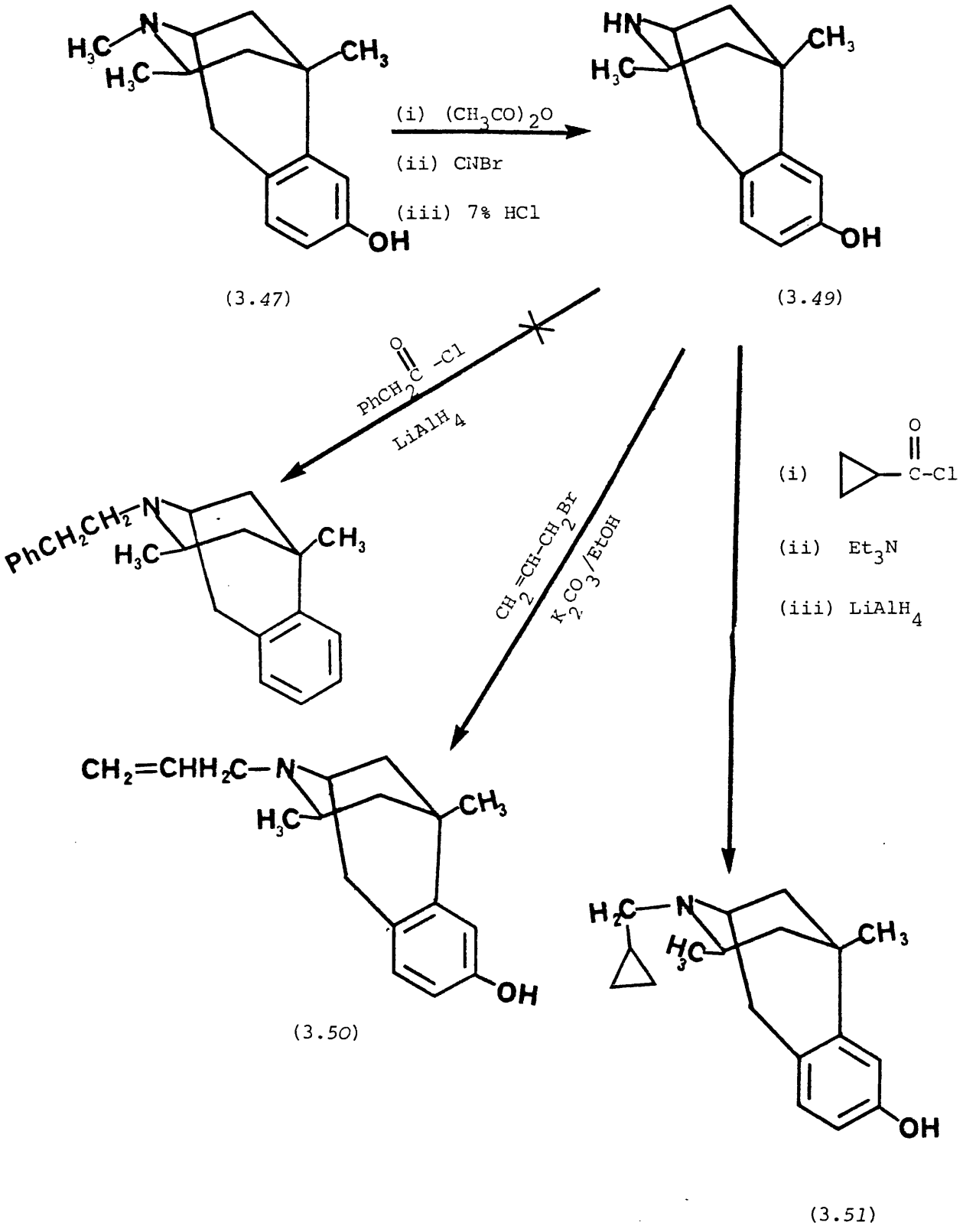
cis and *trans*-isomers in a ratio of about 5:1 respectively. The major isomer, *cis*-2'-hydroxy-6,7-benzomorphan (3.*47*), was obtained as a precipitate after washing the crude oil obtained from cyclisation with ether, but attempts to isolate a pure sample of the minor isomer (3.*48*) from the residue were unsuccessful. The ^{1}H n.m.r. spectrum of pure (3.*47*) was similar to that of the *cis*-isomer of



(3.*47*) $R_1 = CH_3$, $R_2 = H$

(3.*48*) $R_1 = H$, $R_2 = CH_3$

the non-phenolic analogue (3.*5*). This compound displayed a 3-CH_3 resonance, as a doublet, at δ0.93 ppm (entry 2, Table 8) and the corresponding ^{13}C chemical shift was observed at 20.53 ppm. In this and other phenolic benzomorphan analogues prepared, a general upfield shift of the aromatic protons in the ^{1}H n.m.r. spectrum and a distinct downfield shift in the ^{13}C n.m.r. spectrum of the 2'-aromatic carbon, with an associated upfield shift of both C-1' and C-3', was observed.


(i) $(CH_3CO)_2O$
(ii) CNBr
(iii) 7% HCl
(3.47)
(3.49)
$PhCH_2C(=O)-Cl$
$LiAlH_4$
$CH_2=CH-CH_2Br$
K_2CO_3/EtOH
(i)
(ii) Et_3N
(iii) $LiAlH_4$
(3.50)
(3.51)

SCHEME 16

Table 8. ^{1}H chemical shifts of some 2'-OH-6,7-benzomorphan derivatives, in DMSO[a]

Entry	Compound	N-Me	3-Me	4-Me	5-Me
1	3.45	2.24(s)	-	-	1.24(s)
2	3.47	2.26(s)	0.93 (J=6Hz)	-	1.25(s)
3	3.49	-	0.83	-	1.24(s)
4	3.50	b	0.88	-	1.28(s)
5	3.51	c	0.86(d)	-	1.28(s)
6	3.54	2.24(s)	-	0.57(d) (J=6Hz)	1.22(s)

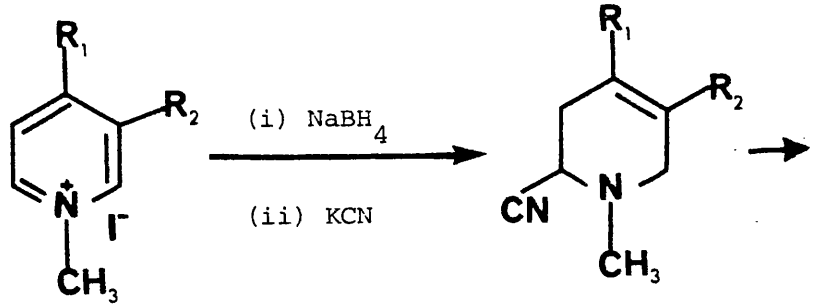
Footnotes to Table 8.

a. Values in ppm from TMS

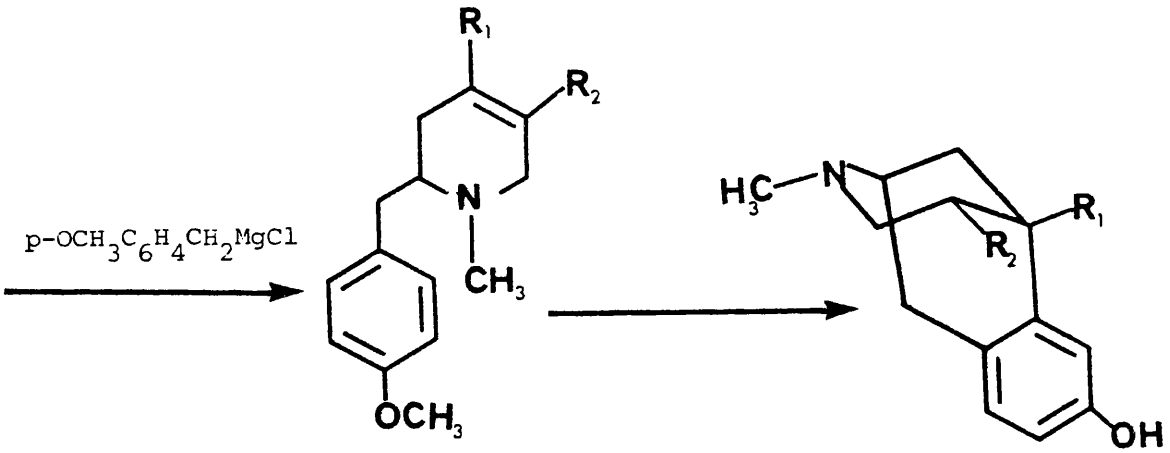
b. The vinylic proton resonances at about 5.80 ppm ($-CH_2-\underline{CH}$), 4.96 - 5.36 ppm ($-CH-\underline{CH_2}$)

c. Cyclopropyl proton resonances at between 0.08 and 0.60 ppm.

Von Braun *N*-demethylation of (3.47) gave 2'-hydroxy-3,5-dimethyl-6,7-benzomorphan (3.49). Compound (3.49) was converted to the corresponding *N*-allyl compound (3.50) by direct alkylation with allyl bromide in ethanol, and to the *N*-cyclopropylmethyl derivative (3.51) by direct acylation with cyclopropylcarboxylic acid chloride and lithium aluminium hydride reduction of the amide intermediate. Attempts to prepare the *N*-phenethyl analogue were unsuccessful (see Scheme 16). The *N*-substituted compounds (3.50 and 3.51) were identified from ^{1}H and ^{13}C n.m.r. characteristics of the *N*-substituents. The *N*-allyl compound (3.50) gave vinylic proton resonance at δ5.80 ppm (m, 1H) and between 4.96 and 5.36 ppm (2H), with corresponding low



(3.52)



(3.53)

(3.54)

$R_1 = R_2 = CH_3$

SCHEME 17

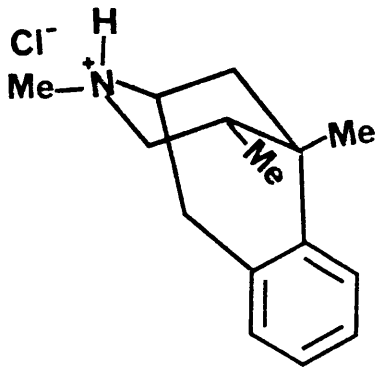
field signals at δ138.04 ppm, due to the vinylic methyne carbon, and δ115.38 ppm due to the vinylic methylene carbon. The *N*-cyclopropylmethyl analogue showed high field multiplets between 0.08 and 0.60 ppm in the ^{1}H n.m.r. spectrum due to the cyclopropyl group protons, and the associated chemical shifts in the ^{13}C n.m.r. spectrum at 2.60, 5.90 and 9.97 ppm, corresponding to the methylene carbons and methyne carbon respectively.

4,5-dialkyl-6,7-benzomorphans

2'-Hydroxy-2,4,5-trimethyl-6,7-benzomorphan was prepared by the method described by Parfitt and Walters[129] for the non-phenolic analogue, using *p*-methoxybenzyl magnesium chloride (Scheme 17). The product (3.*54*) was exclusively that in which the C-4 methyl group is orientated equatorially, thereby lying in the shielding zone of the aromatic ring (Table 8, entry 6). Other ^{1}H and ^{13}C n.m.r. shift values for (3.*54*) are consistent with its structure.

3.3 Pharmacology and Structure-Activity Relationship Correlations

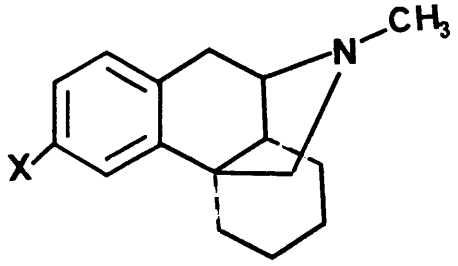
The lower analgesic potency of *cis*-2,3,5-trimethyl-6,7-benzomorphan hydrochloride (3.5 HCl) relative to that of *trans*-2,4,5-trimethyl isomer (3.55), (Table 9, entries 2 and 13), was attributed by Parfitt and Walters[129] to possible hindrance of the nitrogen lone electron pair by the equatorial 3-methyl group of the former. This led to the suggestion that hindrance of the nitrogen lone electron pair may have some bearing on the type and level of analgesic activity exhibited. Since then, many proposals have emerged on the role of



(3.55)

nitrogen lone electron pair in opiate-receptor interactions.

Among these, Belleau *et al*.[179] in explaining the inactivity of *N*-methyl-D-normorphinan (3.56a) and its 3-hydroxyl analogue (3.56b) (which are neither agonist nor antagonist) relative to that of morphinan (3.57) and benzomorphan ring system, have shown the critical importance of the relative orientation of nitrogen electron pair in productive interaction with the opiate receptor. The X-ray analysis

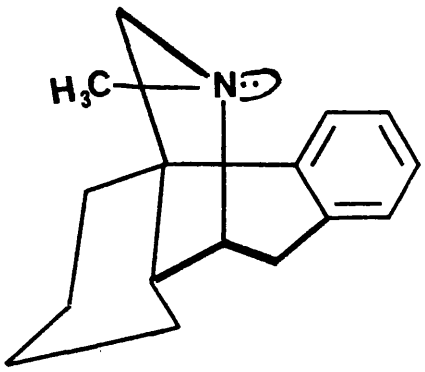


(3.56*a*) X = H

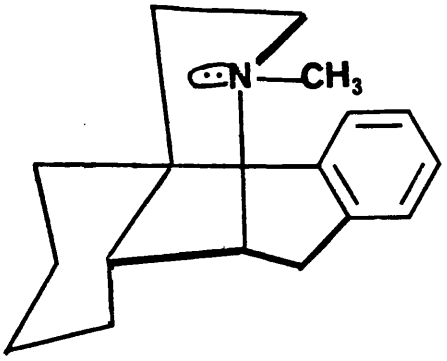
(3.56*b*) X = OH

of the structures of (3.56a) hydrobromide and morphinan (3.57) revealed that the lone pair of the former projects towards the benzene

ring; those of the latter and benzomorphan ring system project away from the benzene ring.



(3.56a)



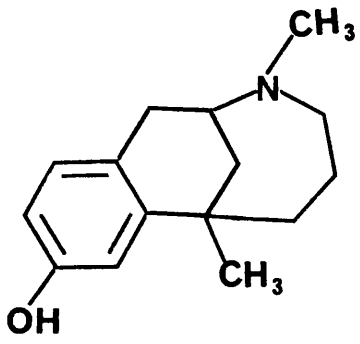
(3.57)

This led to Belleau's theory of "clastic binding", which proposed that the binding of drugs to opiate receptor involved an interaction of the nitrogen lone electron pair with an electrophilic site on the receptor, followed by a stereospecific electron transfer away from the ligand[180]. This view was endorsed by Kolb, who proposed a new opiate-receptor model in which only one conformation of the receptor, with two different spacially fixed amine sites (one agonist and one antagonist), is needed for binding of both agonist and antagonist[181]. The opiates undergo binding to their amine-binding sites *via* the lone electron pair on nitrogen.

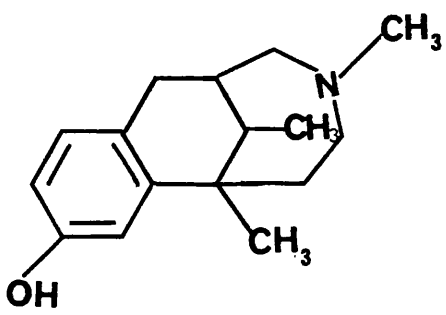
The kind of activity displayed by an opiate according to Kolb, depends on whether the structural influences within the molecule could lead the nitrogen lone electron pair lobe to assume a characteristic directionality needed for binding either to the agonist or antagonist

site. When this direction is not rigorously maintained, a mixed activity ensues.

However, contrary to the above proposals is the generally held belief that the opiate nitrogen interacts with the opiate receptor in its protonated form[42,182]. Furthermore, Shiotani *et al.*[47], reported analgesic activity in a pair of homobenzomorphans (3.*58* and 3.*59*) where electron pair on nitrogen project towards the benzene ring and away from it respectively, and thus came to the conclusion that orientation of the nitrogen electron pair of benzomorphan and morphinan analogues does not account for structurally induced variations in their pharmacological properties.



(3.*58*)



(3.*59*)

From all the above, it is clear that there is no consensus regarding the nature of opiate receptor-ligand interactions. Nevertheless, it would appear that electron density of the nitrogen is relevant to opiate activity.

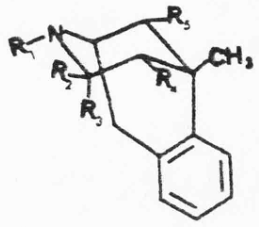
A further investigation of the suggestion by Parfitt and Walters[129]

led to the preparation and analgesic testing (mouse hot plate) of 3,3-disubstituted 5-methyl and 3-monosubstituted 5,9-dimethyl-6,7-benzomorphans. The results of this investigation are illustrated in Table 12.

On the assumption that the pharmacokinetic factors governing drug absorption and transport are uniform for the benzomorphans examined, attempts are made to explain the results obtained in terms of the events at the receptor. Taking 2,5-dimethyl-6,7-benzomorphan hydrochloride as the "parent" compound, insertion of an equatorial 3-methyl group as in 2,3,5-trimethyl-6,7-benzomorphan HCl (3.5) (entry 2, Table 9) gave a small increase in analgesic potency, whereas the axial 3-methyl isomer (3.6 HCl) resulted in a twofold reduction in activity. This reduction in the axial 3-methyl derivative where no hindrance is apparent, suggests that lone pair hindrance in the equatorial 3-methyl compound probably does not affect activity. More importantly, it seems the analgesia observed is more likely to be a function of the overall molecular geometry of the benzomorphan. This assertion is supported by the consistent loss of activity shown by axial 3-alkyl (3.38 and 3.39) and 3-aralkyl (3.40 and 3.41) substituted *cis*-2,5,9-trimethyl-6,7-benzomorphans (cf. entries 8 - 11 with entry 7, Table 9). It is possible therefore, that the differences observed between the 3- and 4-methyl positional isomers by Parfitt and Walters is a result of direct participation of the substituents in binding to the receptor, or accounted for by some other yet unknown molecular factors.

The activities of the 3,3-disubstituted compounds (3.32 - 3.34; entries 4 - 6, Table 9) are accounted for in terms of the contributions

Table 9. Analgesic activity of some 3-monosubstituted and 3-disubstituted 6,7-benzomorphans



Entry	Compound	R_1	R_2	R_3	R_4	R_5	ED_{50} mg/kg	Ref
1	-	CH_3	H	H	H	H	11.05	102
2	(3.5)	CH_3	CH_3	H	H	H	10.6	
3	(3.6)	CH_3	H	CH_3	H	H	24.7	
4	(3.32)	CH_3	$-CH_2Ph$	CH_3	H	H	b	
5	(3.33)	CH_3	$-CH_2CH=CH_2$	CH_3	H	H	3.7	
6	(3.34)	CH_3	CH_3	$-CH_2CH=CH_2$	H	H	c	
7	(3.11)	CH_3	H	H	H	CH_3	13.3	
8	(3.38)	CH_3	H	CH_3	H	CH_3	14.8[e]	
9	(3.39)	CH_3	H	$-CH_2CH_3$	H	CH_3	c	
10	(3.40)	CH_3	H	$-CH_2Ph$	H	CH_3	b	
11	(3.41)	CH_3	H	$-(CH_2)_2Ph$	H	CH_3	b	
12	-	$-CH_2-C-C_2H_5$ CH_3	CH_3	H	H	H	2.2[d]	129
13	(3.55)	CH_3	H	H	CH_3	H	4.2	129
14	Morphine						1.2	129

Footnote to Table 12.

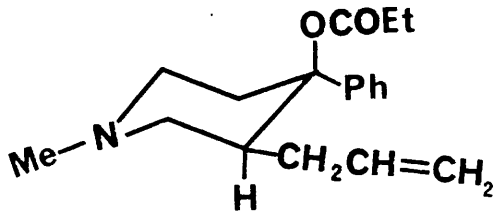
a) The compounds were tested as hydrochlorides for analgesic activity by the Eddy-Leimbach mouse hot-plate procedure employing caesarian derived general purpose mice (CDCP) at the National Institute of Health, Bethseda U.S.A.
b) No-dose response
c) Insufficient activity (toxic)
d) Compound tested as hydrobromide.

of the axial and equatorial substituents, as observed in the mono-substituted compounds. Although synthetic difficulties precluded the preparation of 3,3-dimethyl compound, both the 3-benzyl (3.*32*) and 3-allyl-3-methyl compounds (3.*33* and 3.*34*) were obtained. The lack of activity of 3-benzyl-3-methyl-6,7-benzomorphan (*trans* 3-Me/5-Me, 3.*32*) is not unexpected from an axial methyl group, as in the axial 3-methyl compound (entry, 2, Table 9 , but the lack of data on the equatorial 3-benzyl group prevents the assessment of its contribution towards the activity seen.

In the 3-allyl-3-methyl compounds (entries 5 and 6, Table 9 the axial 3-allyl isomer (*cis* 3-Me/5-Me) showed no activity. This is consistent with an axial orientation of the 3-allyl group in the compound (cf. other axial substituted compounds, entries 8 - 11, Table 9). However, the relatively high agonist activity of the equatorial 3-allyl isomer (*trans* 3-Me/5-Me, 3.*34*) is unexpected, since the axial 3-methyl group should cause about twofold reduction in activity. This observation raises some questions about the role of the equatorial 3-allyl group in receptor interactions, and whether or not the compound (3.*34*) is acting differently at the same receptor as (3.*32* and 3.*33*) or acting at a different receptor.

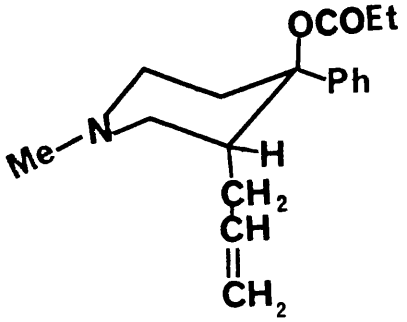
The relatively high potency of the equatorial 3-allyl compound (3.*34*), may be an indication of the large contribution to binding made by the carbon-carbon double bond of the 3-allyl group when present in the equatorial position. Similar observation has been made with the relative potency of 3-allyl prodines, where the equatorial 3-allyl compound (3.*60*) is 13 times, and the axial 3-allyl

(3.*61*) one tenth as active as morphine[30].



(3.*60*)

ED_{50} = 0.09 mg/kg



(3.*61*)

ED_{50} = 11.7 mg/kg

Alternatively, another possible explanation of the higher activity of (3.*34*) over (3.*33*) is to consider the former as a mixed agonist and antagonist similar to nalorphine and pentazocine. In Snyder's proposal to explain the activities of such mixed agonists - antagonists, the *N*-allyl group of the molecule is considered to be flexible and freely rotating, so that at any given time some molecules are in the antagonist form and some are not[40]. An examination of the models of equatorial 3-allyl (3.*34*) and axial 3-allyl compound (3.*33*) revealed that the equatorial 3-allyl group is capable of free rotation whereas, the axial 3-allyl group is hindered by both the benzene ring and the equatorial 3-methyl groups. Considering the proximity of the equatorial 3-allyl group to nitrogen, it is possible that one of the allyl orientations was fixed in a position favourable for interaction with the agonist conformation of the receptor. Compound (3.*34*) is being evaluated for antagonist activity, the result of which will indicate whether an orientation favouring interaction with the

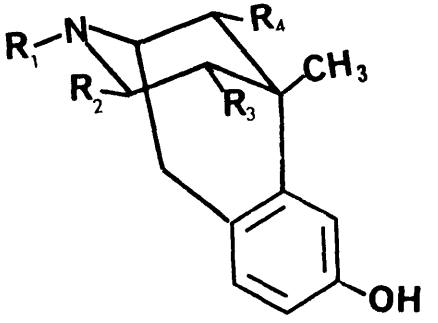
antagonist conformation is possible, and thus support or diminish the application of Snyder's proposal.

It is reasonable to expect an enhanced analgesic potency after the inclusion of a 2'-phenolic hydroxyl group in non-phenolic 6,7-benzomorphans. Thus, phenolic analogues of *N*-alkyl-3,5-dimethyl and 2,4,5-trimethyl-6,7-benzomorphan were prepared and tested. The results are shown in Table 10.

As expected, the *N*-methyl (3.*47*) and *N*-allyl(3.*50*) compounds of *cis*-3,5-dimethyl-6,7-benzomorphans showed an enhanced agonist activity, the former as active as morphine and the latter one quarter as active. However, there was no change in agonist activity of the *N*-cyclopropylmethyl analogue (3.*51*) (cf. entry 12, Table 9 with entry 4, Table 10). This result for (3.*51*) implies that either the phenolic hydroxy group is not properly positioned to take part in the presumed H-bonding receptor interactions leading to higher affinity and intrinsic activity, or its binding in a new receptor location does not contribute significantly to the activity observed. It is also worthwhile to note the high analgesic potency of the *N*-allyl (3.*50*) and *N*-cyclopropylmethyl (3.*51*) derivatives of 2'-hydroxyl-3,5-dimethyl-6,7-norbenzomorphan, compared to the analogous derivatives in the *cis*-5,9-dimethyl isomer (cf. entries 3 and 4 with 6 and 7, Table 10).

Finally, the unexpected loss of activity of the 2'-hydroxyl-analogue of 2,4,5-trimethyl-6,7-benzomorphan (3.*54*) is puzzling (cf. entry 13, Table 9 with entry 5, Table 10). The result suggests

Table 10. Analgesic activity of some 2'-hydroxy-6,7-benzomorphans



Entry	Compound	R_1	R_2	R_3	R_4	ED_{50} mg/kg	Ref.
1	(3.45)	CH_3	H	H	H	5.2	102
2	(3.47)	CH_3	CH_3	H	H	1.1	
3	(3.50)	$-CH_2CH=CH_2$	CH_3	H	H	4.2	
4	(3.51)	$-CH_2-C-C_3H_5$	CH_3	H	H	2.4	
5	(3.54)	CH_3	CH_3	CH_3	H	b	
6		$-CH_2-C-C_3H_5$ [c]	H	H	CH_3	23.1	91
7		$-CH_2CH=CH_2$	H	H	CH_3	d	91
8	Morphine					1.2	102

Footnotes:

a. The compounds were tested as hydrochlorides for analgesic activity by the Eddy-Lembach mouse hot plate procedure at the National Institute for Health (U.S.A.)

b. Insufficient activity (toxic) c. Compound tested as base. d. Inactive

that either there may be different receptors for the phenolic and non-phenolic benzomorphans, or that the molecular geometry responsible for activity of the non-phenolic compound is disrupted by a phenolic 2'-hydroxyl group as in (3.54). If this is the case, the concept of enhanced analgesic activity with introduction of phenolic hydroxyl group into 6,7-benzomorphan will prove not to be of general application.

In summary, from the preparation and pharmacological evaluation of more 3-alkyl monosubstituted (equatorial and axial) and 3,3-dialkyl substituted 6,7-benzomorphans, the potency differences between the 3- and 4-methyl-6,7-benzomorphans, observed by Parfitt and Walters, and between equatorial and axial 3-alkyl isomers as observed in this work, has been explained in terms of substituent participation at the receptor or by some other yet unknown molecular factors, rather than hindrance of the nitrogen lone pair. Furthermore, the relatively high agonist potency of the equatorial 3-allyl-3-methyl-benzomorphan (3.34) encouraged us to examine the possibility of a classical *N*-antagonist substituent, causing a mixed activity at the α-position to nitrogen. Finally, the apparent lack of activity of the 2'-hydroxyl-2,4,5-trimethyl-6,7-benzomorphan relative to its non-phenolic analogue, calls for a further investigation as to whether enhanced activity always results from the introduction of phenolic hydroxyl group into 6,7-benzomorphans (with particular reference to 4,5-disubstituted benzomorphans).

The following suggestions are made for further work to afford more evidence on some of the observations made above.

a) The reduction of the 3-allyl-3-methyl-6,7-benzomorphan (3.*33* and 3.*34*) to the 3-n-propyl analogues, and pharmacological evaluation to ascertain whether the carbon-carbon double bond of the allyl group is contributing to the receptor binding, and hence, the activity observed in the equatorial 3-allyl compound.

b) The preparation and analgesic evaluation of various *N*-substituted derivatives of equatorial 3-allyl-3-methyl compound (3.*34*) with a view to determining if the change in activity is parallel to that seen in equatorial 3-methyl compounds, and hence providing evidence as to whether the two pharmacophores are acting at the same receptor; and finally

c) The preparation and pharmacological evaluation of more nnn-phenolic and phenolic derivatives of 4,5-disubstituted 6,7-benzomorphans, in particular, the 4,5-dialkyl analogues. The objective of this will be to establish whether dialkyl substitution optimal for activity in the 5,9-isomer ($\underline{\alpha}$ and $\underline{\beta}$) has the same effect in this series. In addition, further studies on the role of the 2'-phenolic hydroxyl group are necessary.

CHAPTER 4

Stereochemical Studies of Substituted 6,7-Benzomorphan Derivatives by ^{13}C and ^{1}H NMR Spectroscopy

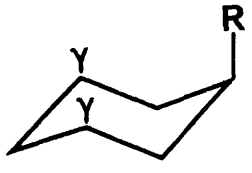
4.1 Introduction

The literature[183] contains evidence of the critical influence of molecular geometry upon analgesic activity of 6,7-benzomorphan derivatives and this makes the establishment of the stereochemistry of novel 6,7-benzomorphans a desirable objective. Both ^{1}H and ^{13}C n.m.r. techniques may be extensively exploited in realising this objective. N.m.r. techniques are of value for identification and differentiation purposes and, in addition, ^{1}H and ^{13}C n.m.r. data provide evidence of the configuration and preferred conformation of molecules. With ^{1}H n.m.r., chemical shift values and coupling constants are of immense value in configurational assignments, while the use of ^{13}C n.m.r. for stereochemical assignment is based on the effects of the various substituents on the ^{13}C chemical shifts of ring carbons of a model parent compound. Generally, these effects depend on both the nature and geometry of the substituents and are not confined to the nearest atom, that is the α-carbon, but extend to γ or δ carbon atoms. In particular, a methyl group deshields α and β-carbon atoms but shields γ ones. In the present work, ^{1}H n.m.r. spectra were obtained on a spectrometer operating at 100 mHz, but higher field spectra (220 mHz) were occasionally necessary. The stereochemical deductions come from ^{1}H and ^{13}C n.m.r. spectra of free bases and are supported, where necessary, by the n.m.r. features of some of the corresponding methiodides. Some lanthanide shift reagent experiments are also reported.

4.2 Configurational studies and structure elucidation

^{13}C chemical shift data for a variety of alkyl-substituted 6,7-benzomorphans are given in Table 11. The carbon atoms in the substituents are identified by a prime on the number appropriate to the position of substitution within the ring system. ^{13}C signal assignments for these molecules are based on comparisons with model compounds (two analyses of morphine alkaloids are of particular relevance in this respect)[184,185], established chemical shift parameters and single-frequency off-resonance decoupled (SFORD) spectra. Use is made of the following stereochemical shift relationships in deductions of configuration and conformation:

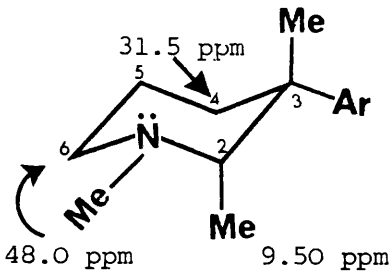
a) The γ-shielding effect[149,150,186-188]. This is the shielding effect on a resonating carbon caused by R groups in a γ-gauche orientation to it (see γ in 4.1).



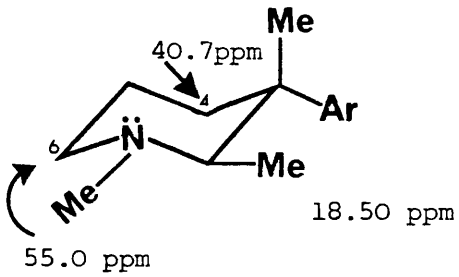
(4.1)

Early attempts[190] to explain its origin attributed it to steric compression between promixate C-H bonds, but more recently[189], a generalised "gauche" n.m.r. effect is thought to contribute in part to the effect. Although its origin is still little understood, the γ-shielding effect has proved to be of considerable value in conformational analysis. For example, in 6-membered alicyclic rings,

γ-gauche alkyl axial substituents produce a sizeable upfield shift of about 3 - 7 ppm, with little or no change in chemical shift of the corresponding equatorial substituent. A typical example is provided by the chemical shifts of C-4 and C-6 of the α-isomer of 1,2,3-trimethyl-3-aryl-piperidine (4.2*a*), which are shielded compared



(4.2*a*), α)



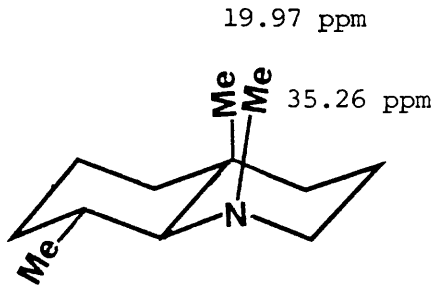
(4.2*b*, β)

to shifts of similar carbon atoms in the β-isomer (4.2*b*)[188].

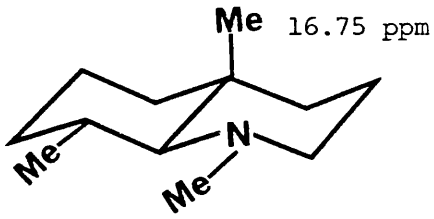
b) The deshielding effects (in ^{13}C) resulting from the interaction of *syn*-diaxially orientated carbons[191,192]. A typical example is shown by the substituted *trans*-decahydroquinoline (4.3*a*), where the methyl shifts are downfield of the corresponding shifts in (4.3*b*) and (4.3*c*)[191]

c) The shielding influence of a nitrogen lone pair orbital on the ^{13}C shift of an α-methyl, when a Me-lone pair antiperiplanar relationship obtains[150,188]. Lone pair shielding of this type has been discussed by Eliel and Pietrusiewicz[191] for some *N*, 2α- and *N*-2β-dimethyl *trans*-decahydroquinolines. Further example is provided

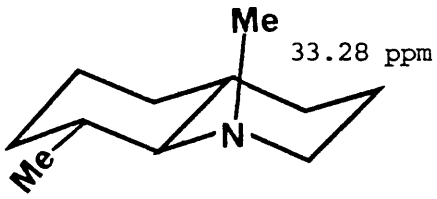
by the isomers of 1,2,3-trimethyl-3-aryl-piperidine (4.2*a* and 4.2*b*), where the shielding influence of the nitrogen lone pair moves the C-2 axial methyl chemical shift in (4.2*a*) upfield relative to the corresponding shift of the equatorial 2-methyl analogue (4.2*b*)[188].



(4.3*a*)



(4.3*b*)



(4.3*c*)

d) The anisotropic shielding influence of an aromatic ring (in ^{1}H n.m.r. spectroscopy), especially on the protons of alkyl substituents lying within the six-fold axis of ring[117,148,151].

Table 11. ^{13}C chemical shifts of some 6,7-benzomorphan derivatives[a]

Entry	Compound	C-1	C-3	C-4	C-5	C-6[b]	C-8	C-9	C-2'	C-3'	C-5'	C-9'
1	4.*4b*(α)	52.87	42.69	39.38	36.89	142.8	32.07	42.36	-	-	25.95	14.09
2	4.*4c*(α)	59.86	47.73	41.93	35.97	142.8	23.02	41.56	42.42	-	25.41	14.19
3	3.*11*(α)[c]	59.48	47.46	42.53	35.86	141.8	23.62	42.09	42.74	-	25.46	14.09
	in DMSO-d_6	58.40	46.86	42.04	35.37	141.5	23.02	41.39	42.42	-	25.19	13.81
4	4.*4d*(α)	57.18	45.04	42.04	35.94	142.3	23.16	41.21	d	-	25.27	13.84
	in DMSO-d_6											
5	4.*4e*(α)	57.21	45.72	41.61	36.46	142.9	23.46	40.96	e	-	25.41	14.19
6	4.*4g*(β)	61.00	48.27	(35.21)	(35.32)	146.4	28.01	39.06	43.12	-	24.22	15.17
7	4.*4f*(β)	53.69	39.33	36.68	35.70	146.0	34.51	37.16	-	-	24.81	14.41
8	3.*5*	56.99	51.57	51.84	34.62	146.0	29.36	41.71	41.17	22.10	29.63	-
9	3.*6*	53.63	51.36	47.57	30.99	146.5	32.56	39.08	40.36	16.79	29.74	-
10	3.*36*	59.81	48.76	46.37	35.92	140.0	23.73	41.06	41.34	f	24.87	13.81
11	3.*38*	59.01	51.75	48.83	34.58	144.0	27.38	40.16	40.81	16.59	26.83	13.89
12	3.*39*	(59.00)	(59.70)	43.94	34.67	143.6	28.01	(40.52)	(40.90)	g	26.82	13.87
13	3.*40*	(58.56)	(60.19)	41.56	34.62	143.6	27.36	42.31	40.74	h	26.65	13.81
14	3.*41*	(59.00)	(57.48)	43.99	34.78	143.5	28.17	41.01	40.63	i	26.76	13.87

/contd....

Table 11 (continued)

Entry	Compound	C-1	C-3	C-4	C-5	C-6[b]	C-8	C-9	C-2'	C-3'	C-5'	C-9'
15	3.*26*	54.93	53.04	52.28	31.85	141.6	28.77	40.14	36.95	28.22[j]	29.90	-
16	3.*32*	54.72	55.47	49.95	32.02	145.1	30.34	40.79	34.78	20.75[k]	29.74	-
17	3.*33*(α)	54.55	55.26	48.81	32.29	144.9	30.83	37.98	34.62	(30.23)[l]	(29.85)	-
18	3.*34*(β)	(54.66)	(54.50)	48.54	32.18	145.5	30.50	40.96	34.35	20.48[m]	29.69	-
19	3.*17*	61.76	188.09	51.79	30.28	141.50	33.75	34.29	43.01	23.84	26.55	-
20	3.*29*	52.87	48.16	48.92	31.42	147.13	35.38	40.90	N-CH$_2$ 36.41	18.74	30.01	-
21	3.*30*	51.14	49.79	46.59	31.26	146.11	32.88	39.22	O	16.63	29.52	-
22	3.*37*	(61.65)	(56.40)	46.10	36.73	142.47	24.70	41.88	39.55	p	25.62	13.81
Methiodides in DMSO-d_6												
23	4.*4c*(α)	69.07	55.85	35.65	34.45	139.8	24.22	33.53	53.09(eq) 50.59(ax)	-	23.35	13.38
24	4.*4g*(β)	70.26	57.32	32.29	33.91	143.3	29.69	37.27	54.72(ax) 52.55(eq)	-	22.54	17.44
25	3.*5* (α)	66.73	59.65	37.81	31.05	141.9	29.03	32.10	43.03(ax) 49.79(eq)	14.14	25.46	-
26	3.*6* (β)	65.23	63.28	40.47	29.20	143.5	30.28	32.88	54.72(ax) 48.81(eq)	17.01	27.30	-
27	3.*38*	69.78	63.33	42.31	32.70	140.8	25.73	33.32	53.93(ax) 48.25(eq)	17.17	24.65	12.95
28	3.*40*	69.83	68.21	(34.18)	33.15	140.6	25.73	33.64	54.65(ax) 48.93(eq)	q	24.65	12.73

Footnotes to Table 12.

a). Bases in $CDCl_3$ or $CDCl_3$-MeOH (4.*4b*, 4,*4c*, 4.4*f* and 4.*4g*) and methiodides in DMSO-d_6 unless otherwise stated; chemical shifts in ppm from TMS (shifts in parentheses may be interchanged)

b). Aromatic carbon resonances fell in the range 147 - 112 ppm; phenolic derivatives displayed a resonance near 156 ppm due to $\underline{C}_{Ar}$ - OH.

c). Non-phenolic analogue of 4.*4c*.

d). C-1 (56.41) and C-2 (34.10 ppm) of *N*-phenethyl substituent.

e). *N*-3,3-Dimethylallyl resonances (ppm): terminal methyls 18.04 and (25.95), C-1 52.39, C-2 121.0, C-3 135.3.

f). 3-$\underline{C}$N resonance 119.62 ppm.

g). 3-Et resonances: CH_2 21.89, Me 12.19 ppm.

h). 3-$\underline{C}H_2$Ph resonance 34.83 ppm.

i). 3-$\underline{C}H_2\underline{C}H_2$Ph resonances 31.3 and 34.08 ppm respectively.

j). 3-$\underline{C}$N resonance 119.5 ppm.

k). 3-$\underline{C}H_2$Ph resonance 51.74 ppm.

l). 3-Allyl resonances (ppm): C-1 41.44, C-2 125.7, C-3 116.8.

m). 3-Allyl resonances (ppm): C-1 51.68, C-2 125.7, C-3 116.7.

Footnotes to Table 12 (continued)

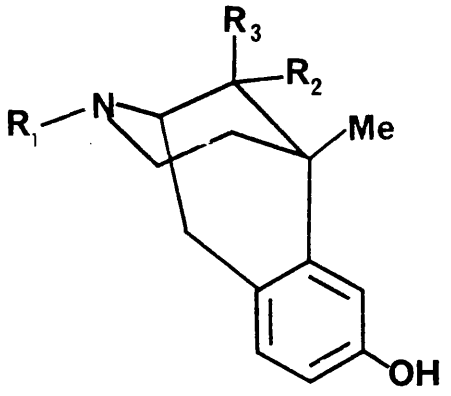
n). *N*-$CH_2\underline{C}N$ resonance at 116.42 ppm.

o). The ethylene diamine carbon resonances $H_2{}^{1}NCH_2{}^{2}CH_2{}^{2}$-N occurred at 39.82 and 54.34 ppm respectively

p). 3-$\underline{C}H_2NH_2$ resonance: 43.88 ppm

q). 3-$\underline{C}H_2$Ph resonance: 35.54 ppm.

9-Methyl derivatives of the 6,7-benzomorphan (4.*4a*) are first discussed. The secondary amine (4.*4b*) (Table 11, entry 1; p.110) is viewed as the parent and model for the series, because the stereochemistry of derivatives related to it is well established.



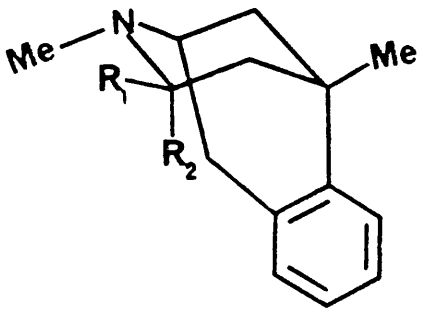
(4.*4*)

	R_1	R_2	R_3	Configuration*	Generic name
a)	H	H	H		
b)	H	Me	H	*cis*-	
c)	Me	Me	H	*cis*-	α-metazocine
d)	$Ph(CH_2)_2$			*cis*-	p-hexazocine
e)	$Me_2C{=}CHCH_2$	Me	H	*cis*-	Pentazocine
f)	H	H	Me	*trans*-	
g)	Me	H	Me	*trans*-	β-metazocine

The assignment of a *cis*-5,9-configuration to the major isomer (4.*4c*) is supported by rates of quaternisation measurements[117], ^1H n.m.r. analyses[117, 151] and, in the case of the 2-allyl derivative, X-ray crystallographic studies[193]. (Entry numbers refer to Table 11 unless otherwise stated). Chemical shift assignments of (4.*4b*) were mostly

trivial. The quartet centred on 25.9 ppm in the off-resonance spectrum was assigned to C-5 methyl carbon and this assignment is confirmed by the presence of a resonance near 26 ppm in all spectra (an equatorial 5-methyl substituent is common to all derivatives). The assignment of the highest field triplet (32.1 ppm) to C-8 was supported by the pronounced upfield shift of this resonance (23.02 ppm) seen after *N*-methylation (entry 2), a consequence of the γ-effect of an equatorial *N*-methyl group. Similar shifts of the analogous C-10 carbon of certain *N*-desmethylmorphine derivatives have been noticed after *N*-methylation[184]. Derivatives of clinical importance - α-metazocine (4.*4c*), phenazocine (4.*4d*) and pentazocine (4.*4e*) - are distinguished by resonances due to the *N*-substituents (entries 2, 4 and 5). In addition, compounds (4.*4d*) and (4.*4e*), with *N*-alkyl substituent larger than methyl, also showed a slight upfield shift at C-3 due to the additional γ-effect. The C-4 chemical shifts of the two *trans*-(β)-5,9-dimethyl derivatives (4.*4f* and 4.*4g*) (entries 6 and 7) are upfield, and those of C-6 and C-8 downfield, of the corresponding resonances of the *cis*-analogues (4.*4b* and 4.*4c*), in confirmation of the axial orientation of C-9 methyl in the former compounds. Axial 9-methyl has a γ-shielding influence at C-4, while the same effect of equatorial 9-methyl at C-6 and C-8 in the *cis*-derivative is absent. Unlike the corresponding 9-methyl proton shift data[117,151], the C-9 ^{13}C shifts of the α/β pairs do not provide any stereochemical information.

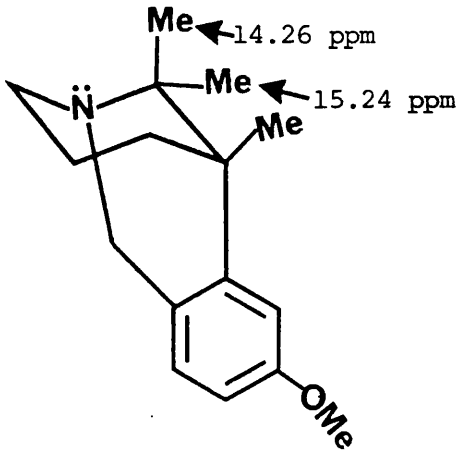
The diastereoisomeric non-phenolic 3,5-dimethyl analogues of 4.*4a* (3.5 α, major; and 3.6 β, minor) are considered next. The pronounced proton chemical shift difference between the α and β-3-methyl protons (α ≃ 0.9, β ≃ 0.5 ppm) points to the minor isomer



(3.5) R_1 = Me; R_2 = H

(3.6) R_1 = H; R_2 = Me

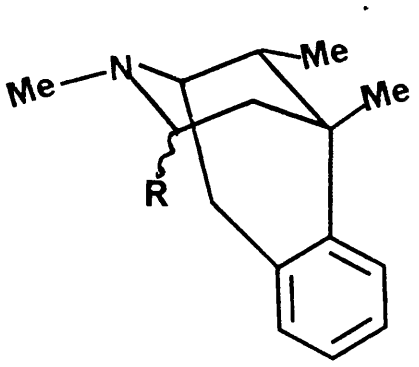
having a *trans* 3-Me/5-Me configuration (with respect to the piperidine ring) since the 3-methyl is positioned well within the shielding zone of the aromatic ring. This conclusion is confirmed by ^{13}C n.m.r. analysis of the two isomers (entries 8 and 9). For the major isomer (3.5), the assignment of the two methine carbon resonances (C-1 57.0, C-3 51.6 ppm) was made by comparison with the corresponding shift data for the α-5,9-dimethyl analogue (entry 2), while of the three triplet resonances (51.8, 41.7 and 29.4 ppm), the highest field is clearly due to C-8, and the lowest field to C-4 (cf. C-8 of β-metazocine and C-4 of α-metazocine, entries 6 and 2 respectively). The chemical shift of C-9 of the benzomorphan skeleton is little affected by methylation, contrary to an expected α-deshielding effect (compare entries 2 and 8). Such an anomaly has previously been noted for piperidine derivatives with 3,4-dimethyl substituents and this has been attributed to ring deformations caused by the relief of gauche interactions between vicinal methyl groups[194]. In the minor isomer (3.6), the C-1 and C-5 resonances are shifted upfield by approximately 3.5 ppm, and the C-8 resonance is 3.2 ppm downfield of the corresponding shifts of the major isomer (entries 8 and 9), in support of an axial orientation of the 3-methyl which would have a γ-shielding influence at C-1 and C-5 and a 1,3-*syn*-diaxial deshielding effect at C-8. The pronounced difference in chemical shift between the 3-methyl resonances (α 22.1, β 16.7 ppm) provides a further example of the shielding influence of a nitrogen lone pair orbital when in an antiperiplanar relationship to methyl, as in (3.6)[150,188]. In the related isomeric 9-methyl-1-azabenzomorphan pair (4.5)[195], both with a gauche methyl-lone pair orientation, the chemical shift difference between the axial and equatorial methyl carbon is minor.



(4.5)

In the case of (3.5) and (3.6), aromatic shielding may also contribute to the chemical shift difference between α and β-3-methyl resonances.

The next group of substituted 6,7-benzomorphans for consideration are the 3-alkyl-5,9-dimethyl derivatives (3.*38*- 3.*41*) prepared from 3-cyano-5,9-dimethyl-6,7-benzomorphan (3.*36*). In both the precursor and products, mixtures of diastereoisomers are produced as judged from the n.m.r. spectra of the total solid product, but the following n.m.r. analyses refer to the major isomers, isolated in pure form, in all cases. The ^{13}C n.m.r. features of the cyano compound (3.*36*) are similar to those of α-metazocine (4.*4c*) and compound (3.*11*) (cf. entries 2, 3 and 10), except for the C-3 and C-4 shifts which are to lower field as anticipated from the deshielding influences of the cyano substituent. The relative magnitudes of shielding, α + 1.03 and β + 4.44 ppm is indicative of an equatorial cyano group[196a]. More evidence from vicinal coupling constant measurements



(3.*11*) R = H

(3.*36*) R = CN

(3.*38*) R = Me

(3.*39*) R = Et

(3.*40*) R = CH_2Ph

(3.*41*) R = CH_2CH_2Ph

(^3J values) between the C-3 position and the 4-CH_2 was sought to corroborate this assignment.

It has been established that the most important factor influencing vicinal HH couplings ($^3J_{HH}$) is the dihedral angle (Φ) between the protons. Φ is the angle between the planes containing the C-C-H' bonds and that containing the C-C-H bonds. The relationship between vicinal coupling constant (^3J) and Φ is illustrated in Figure 2.[197] This representation implies that ^3J values will be largest when vicinal protons are *trans*- coplanar ($\phi = 180^o$), slightly smaller when they are *cis*-coplanar ($\phi = 0$), and around zero when the protons are at right angles.

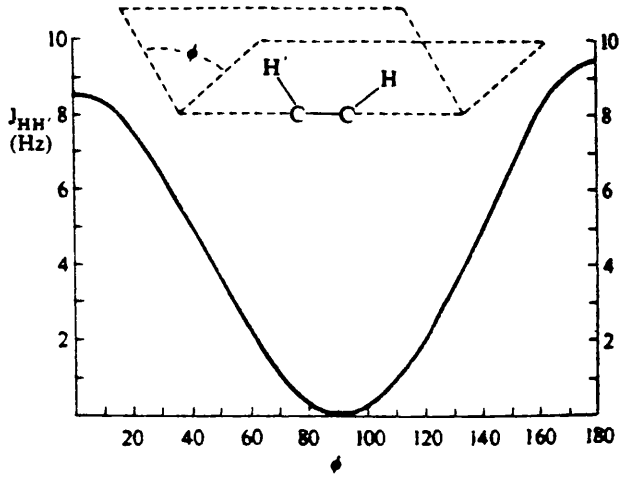


Figure 2. Relationship between the dihedral angle, ϕ , and vicinal coupling constants [197].

One of the most important consequences of this relationship is that the order of magnitude of diaxial, axial-equatorial and diequatorial coupling constants ($^3J_{aa}$, $^3J_{ae}$ and $^3J_{ee}$ respectively), in a piperidine ring chair system can be predicted from a knowledge of ϕ. The ^3J coupling constants generally fall within the ranges 8 - 14 Hz for $^3J_{aa}$ and 1 - 6 Hz for $^3J_{ae}$ and $^3J_{ee}$ [198]. The ^3J data obtained by measurement of dihedral angles and estimation of associated vicinal coupling constants concur with the observed values, and indicate a *cis* 3-CN/5-Me configuration for (3.*36*). The axial C-3 proton in (3.*36*) is expected to couple with one axial and one equatorial proton at C-4. Hence, the coupling pattern for the 3-H_a

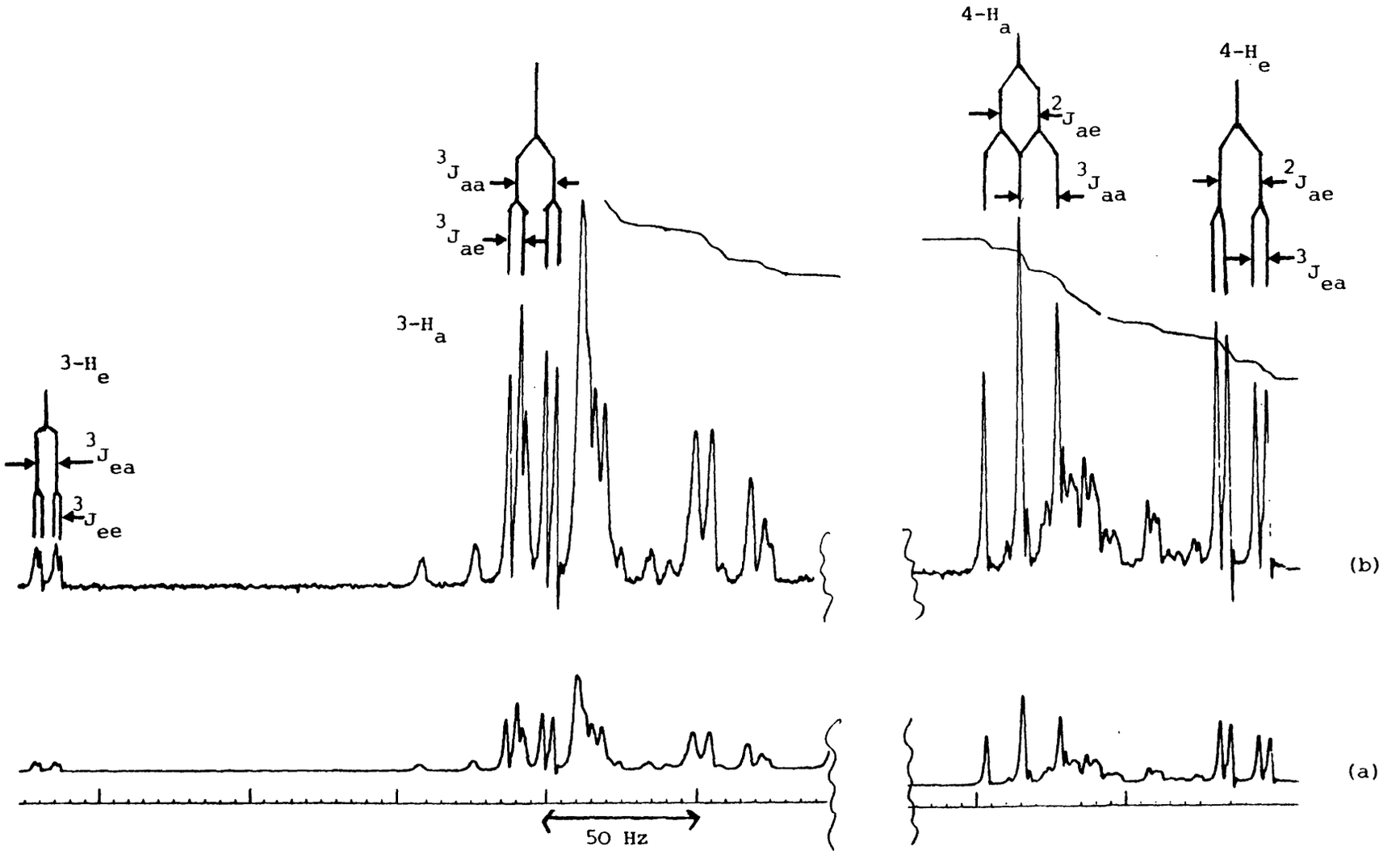
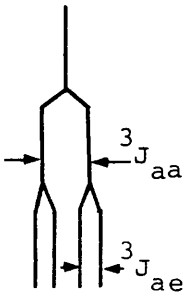
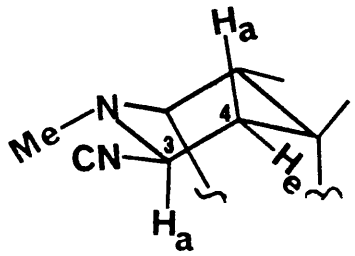


Fig. 3. Portion of the 220 mHz ^{1}H n.m.r. spectrum of 3-cyano-2,5,9-trimethyl-6,7-benzomorphan, (a) sensitivity X1 and (b) sensitivity X4.

is expected to be a doublet of doublets, arising from the C-3 axial hydrogen and 4-Ha doublet (J = 8 - 14 Hz), each of which would be split again into a doublet by the adjacent C-4 equatorial hydrogen (J = 0 - 6 Hz).





(3.*36*, partial formula)

A 220 mHz spectrum of 3.*36* (Fig. 3; partial reproduction) revealed a well resolved doublet of doublets near 3 ppm ($^3J_{aa}$ 12 Hz, $^3J_{ae}$ 3.5 Hz), typical of axial-axial and axial-equatorial proton coupling, a broad triplet at 2.02 ppm (^2J and ^3J about 12 Hz) and a doublet of doublets at 1.68 ppm (^3J 3.5 Hz, ^2J 12 Hz), which are reasonably attributed to 3-H_a/4-CH_2 protons. Of the three multiplets specified above, the higher field pair were resolved at 100 mHz (Fig. 4a); all three became resolved and shifted downfield in the presence of excess lanthanide shift reagent Eu(fod)$_3$ (Fig. 4b), as did the minor signals, such as the low intensity 9-methyl doublet together with a low-field multiplet near 4.5 ppm (with separation 5 Hz) that is probably due to 3-H_e of the axial 3-cyano component (see Fig. 3). The isomeric nature of the cyano derivative, even after further recrystallisations, was confirmed by a long run ^{13}C n.m.r. spectrum which showed several low intensity resonances that were absent in a spectrum recorded after a normal run (1000 - 2000 scans).

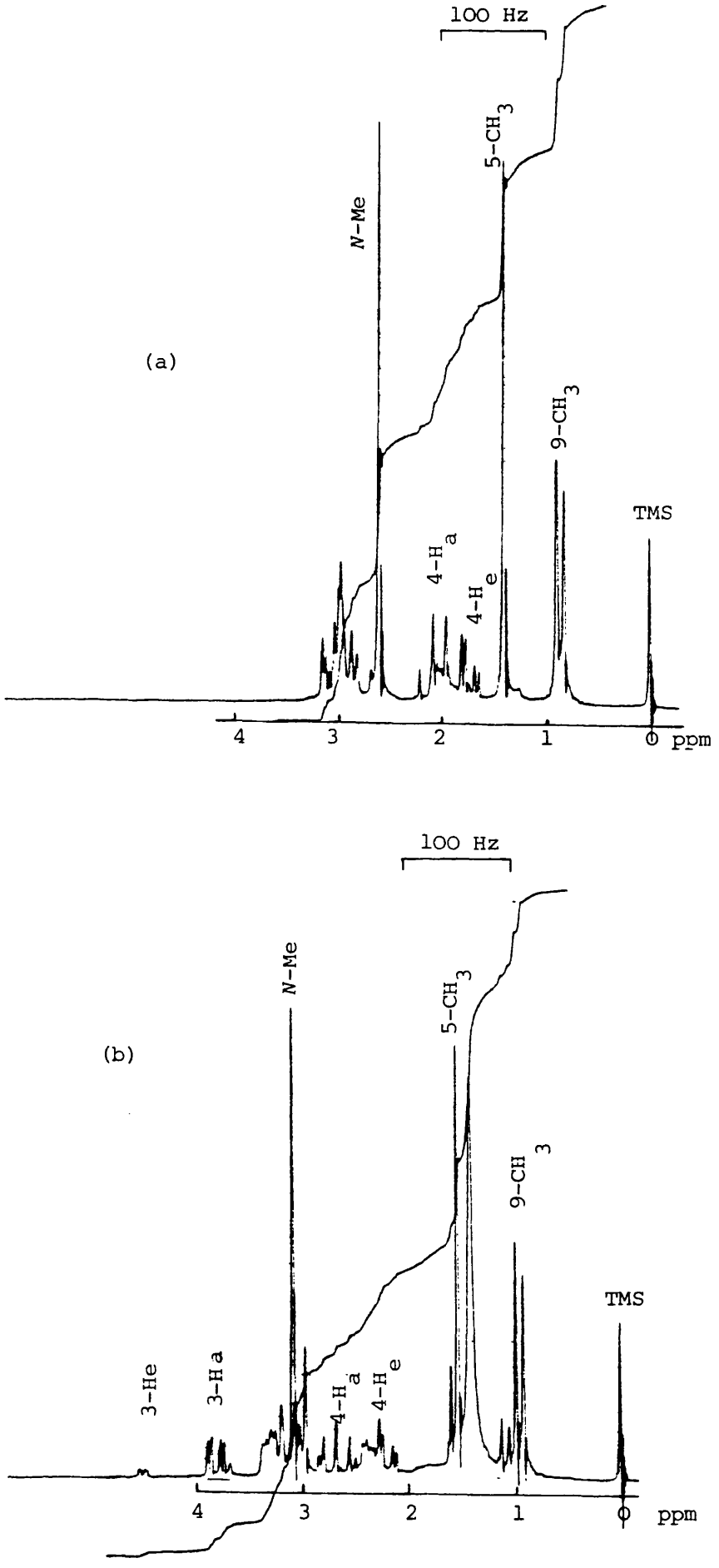


Fig. 4. Portion of 100 mHz ^{1}H n.m.r. spectrum of 3-cyano-2,5,9-trimethyl-6,7-benzomorphan; (a) in $CDCl_3$ (b) after addition of $Eu(fod)_3$, 34 mg in $CDCl_3$.

Clear evidence of an axial orientation of C-3 methyl in (3.*38*) is its high field ^{1}H (0.42 ppm) and ^{13}C (16.5 ppm) resonances relative to the 3-methyl shifts of the isomeric 3,5-dimethyl derivatives (entries 8, 9 and 11), and the lowfield C-8 chemical shift (27.4 ppm) compared with the C-8 shift (23.0 ppm) of α-metazocine (entry 2) which is a result of *syn*-diaxial deshielding. γ-Shielding effects of the axial 3-methyl at C-1 and C-5 are unusually low, as judged by the corresponding shifts of α-metazocine and 3.*6* (entries 2, 9 and 11), and suggest some deformation of the tri- compared with the di-C-methyl substituted molecules. Data in the 3-ethyl analogue 3.*39* (entry 12) also support a *trans*-3-R/5-Me configuration with an axial substituent at C-3. The evidence comes from correct assignment of the two higher field triplets, achieved by selective decoupling experiments. In a selective decoupling experiment, the proton resonances due to the carbons in question is identified in the ^{1}H n.m.r. spectrum. These protons are then completely irradiated at low radio frequency power. The result observed in ^{13}C experiments is that the carbon attached to such protons collapses to a singlet, while other protonated carbons retain some C-H coupling[199]. For (3.*39*), the proton irradiation at the C-8 benzylic proton resonance near 2.8 ppm resulted in an intense singlet at 28.0 ppm and a broadened signal at 21.8 ppm indicative of a residual C-H coupling (Fig. 5b); similar irradiation at the $MeCH_2$ resonance near 1.8 ppm produced the reverse effects. Thus, the 28.0 ppm triplet in the off-resonance spectrum of (3.*39*) could be unequivocally assigned to C-8, and the signal at 21.8 ppm to the C-3 ethyl methylene carbon. All shifts except those of the 3-R substituents thus correspond closely for spectra of (3.*38* and 3.*39*), while the methylene carbon of 3-Et of (3.*39*) had an

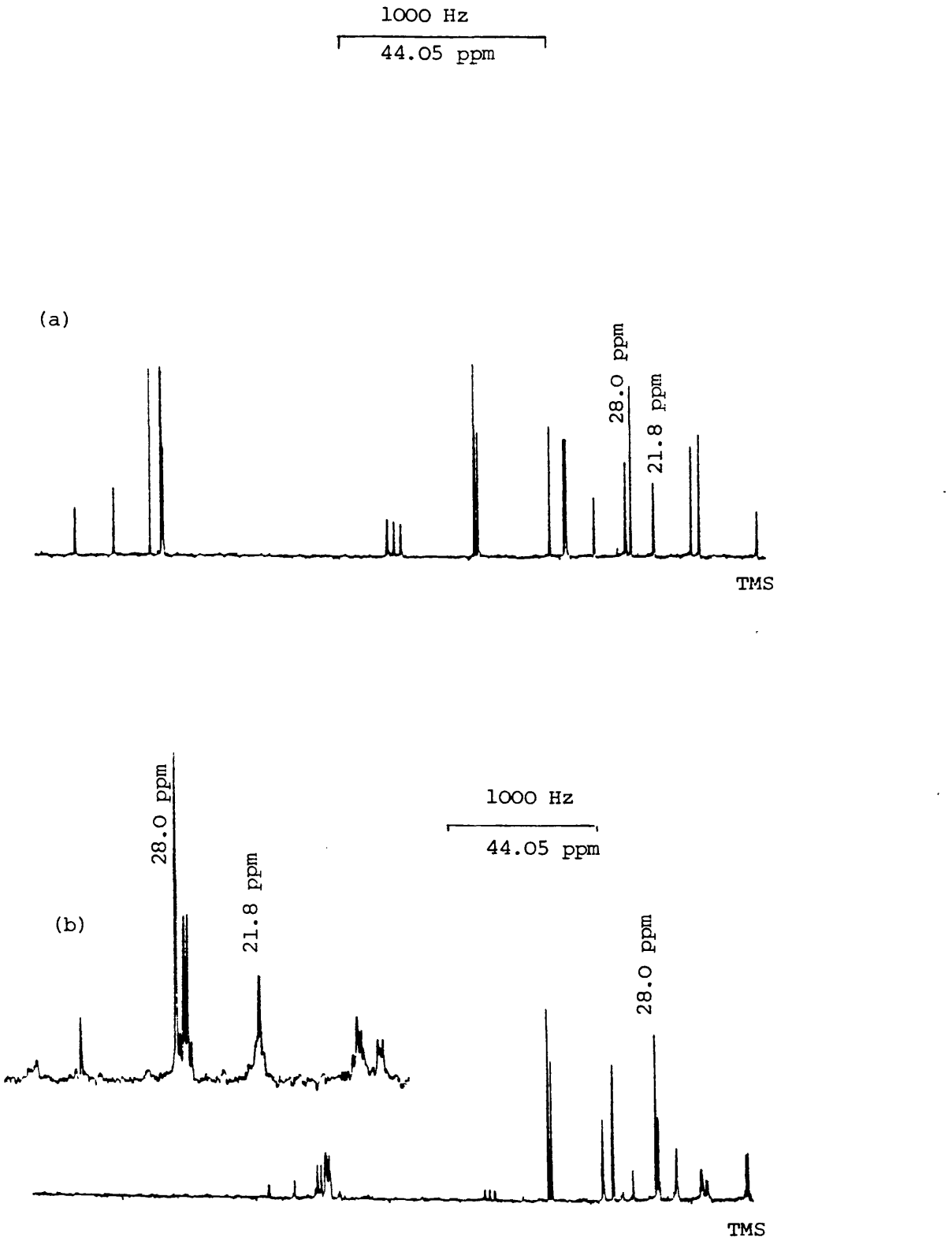
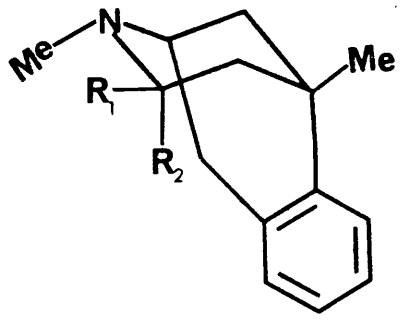


Fig. 5. Data from a selective ^{13}C decoupling experiment of the C-8 benzylic methylene carbon protons in 3-ethyl-2,5,9-trimethyl-6,7-benzomorphan. (a) Proton noise decoupled spectrum (b) selectively decoupled spectrum.

unusually high field chemical shift in accord with its axial orientation and antiperiplanar relationship to the nitrogen lone pair orbital. This high field shift of the methylene carbon of 3-Et becomes more apparent when it is compared with the corresponding data on 3-ethylcyclohexane (δ $\underline{C}H_2$ Me, 31.0 ppm)[196b]. Similar arguments support a *trans*-3-R/5-Me configuration for the 3-benzyl and 3-(2-phenethyl) analogues (3.*40*) and (3.*41*) (entries 13 and 14 respectively).

The final group of derivatives are the 3-substituted-3,5-dimethylbenzomorphans (3.*32*- 3.*34*), obtained from the 3-cyano analogue (3.*26*).



(3.*26*) $R_1 = CH_3$, $R_2 = -CN$

(3.*32*) $R_1 = CH_2Ph$, $R_2 = Me$

(3.*33*) $R_1 = CH_3$ $R_2 = -CH_2CH=CH_2$

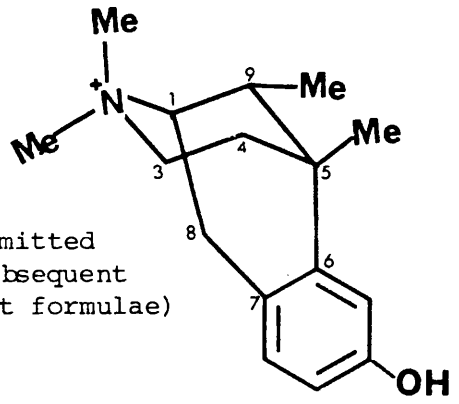
(3.*34*) $R_1 = -CH_2CH=CH_2$, $R_2 = Me$

General points about the ^{13}C n.m..r. features of (3.*26*, 3.*32* - 3.*34*) (entries 15 - 18) are the shifts of the *N*-methyl and C-3 resonances

to higher and lower field respectively, compared with the corresponding shifts of the other derivatives (3.5 and 3.6), a result of the disubstitution at C-3; two γ-effects at N-$\underline{C}H_3$ and two α-effects at C-3. The shifts of the C-1, C-5 and C-8 carbons provide no information on the stereochemistry in these cases, since all derivatives carry axial substituents at C-3. Clear evidence of the stereochemistry was provided, however, by the ^1H n.m.r. spectra of the major (α) and minor (β) 3-allyl derivatives, which were both isolated in a pure state. Comparative shift values of the 3-methyl protons (α 1.05, β 0.32 ppm) and vinylic protons of the 3-allyl group (α near 5.2, 4.1; β near 5.8, 5.0 ppm, Table 7) established the *cis*-3-Me/5-Me configuration of the major isomer with an equatorial methyl group at C-3. The axial orientation of the 3-allyl in the same isomer is substantiated by the vinylic chemical shifts, which are to higher field of those of the β-isomer as a result of aromatic shielding. It is also consistent with the assignment of α(*cis*)- and β(*trans*)-3-Me/5-Me that the α-C-3' ^{13}C chemical shift should be to lower field, and the α-methylene carbon of the allyl group to higher field, than the corresponding β-resonances (entries 17 and 18). The 3-benzyl derivative (3.32) is assigned a *trans*-3-Me/5-Me configuration on the basis of its 3-methyl proton shift (near 0.38 ppm). Other ^{13}C n.m.r. features, notably the C-3' shift of 20.75 ppm, are close to those of the β-3-allyl derivative of the same configuration. Finally, the 3-cyano derivative (3.26) with a 3-methyl proton chemical shift near 1.3 and a ^{13}C shift of 28.2 ppm (both comparatively low field values) is assigned the *cis*-configuration with an axial cyano substituent.

Quaternary Salts

The value of quaternary salt n.m.r. data as an aid to the configurational assignment of substituted piperidines has recently been demonstrated[192]. Hence, spectra of methiodides of some of the present 6,7-benzomorphan derivatives have been analysed to corroborate the stereochemical deductions drawn from the study of the bases. The methiodide of α-metazocine (4.*4c*) is the model for the quaternary salt series.



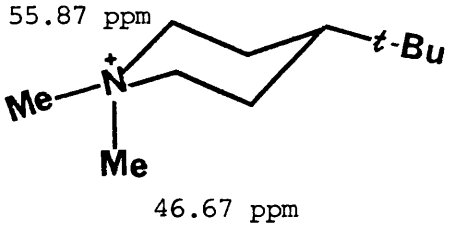
(Iodide anion omitted in this and subsequent quaternary salt formulae)

(methiodide of 4.*4c*)

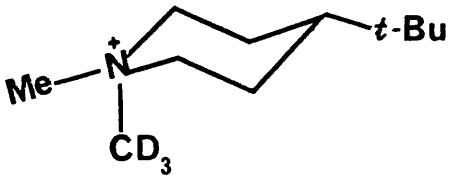
Although spectra of bases were obtained from solutions in $CDCl_3$ and the salts from solutions in DMSO-d_6, the free base-quaternary salt ^{13}C data may be compared as solvent effects are considered negligible as judged by the essentially identical chemical shift data on the non-phenolic analogue of (4.*4c*, entry 3) in both $CDCl_3$ and DMSO-d_6 solvent.

Free base-quaternary salt ^{13}C n.m.r. comparisons (entries 2 and 23) show that *N*-methylation of (4.*4c*) produces downfield shifts

at C-1 and C-3 (β-effect of additional *N*-Me) and C-8 (+1.2 ppm, deshielded by antiperiplanar *N*-Me), and upfield shifts at carbons 4-6, 9-, 5' and 9'. The upfield effects are attributed to the positive charge on nitrogen (as in *N*-protonation)[200,201] and, at C-4 and C-9, to the γ-effect of the axial *N*-methyl group. Of the two *N*-methyl resonances, the one at higher field (50.6 ppm) is assigned as axial since it is subject to greater steric polarisation. The lower field resonance (53.1 ppm) is associated with the equatorial group. This assignment is supported by comparison of the spectra of the methiodide (4.6*a*) and the corresponding trideuteromethiodide (4.6*b*) of 4-*t*-butyl-1-methyl-piperidine[202]. The higher field *N*-methyl resonance of (4.6*a*) was absent in the spectrum of (4.6*b*). This missing signal must therefore be due to the axial *N*-substituent, because the axial *N*-CD_3 isomer will preponderate in (4.6*b*)



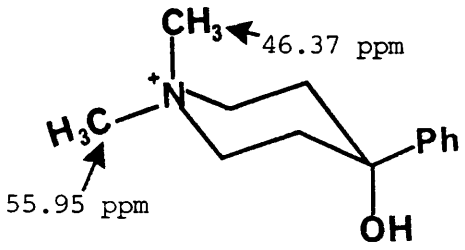
(4.6*a*)



(4.6*b*)

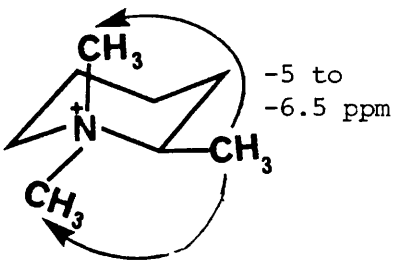
as expected from a preferred axial course of methylation of an equatorial *N*-alkyl conformer[167]. A typical feature of all *N*-methyl resonances in the spectra of the methiodides examined was their broad nature, a result of *N*-C couplings[203]. The difference between the *N*-methyl shifts of ametazocine methiodide and those of the

methiodide of simple piperidines such as, 1-methyl-4-phenyl-4-piperidinol (4.7) may be explained by the presence of an α-axial carbon C-8 in the benzomorphan.

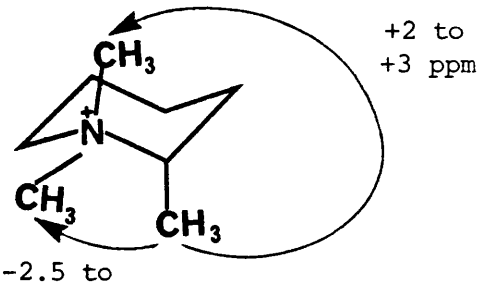


(4.7)

Previous studies[192] of simple mono- and di-C-methyl derivatives of *N,N*-dimethylpiperidinium iodide show that α-equatorial methyl shields both *N*-methyl carbons, with greater effect upon the axial group (4.*8*), while α-axial methyl shields equatorial *N*-methyl and deshields axial *N*-methyl (4.9).



(4.*8*)

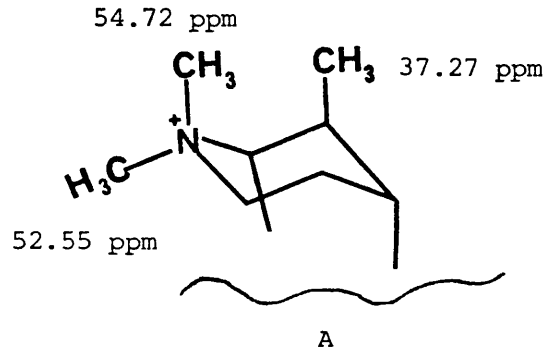


(4.*9*)

The upfield shifts observed is attributed to steric compression resulting from γ-gauche interactions, but the basis of antiperiplanar Me/Me deshielding is little understood. Similar shielding influences

of α-methyls on the *N*-methyl ^{1}H resonances of piperidinium salts have also been observed[204].

The chemical shift data for β-metazocine methiodide (entry 24) are consistent with the retention of the piperidine chair conformation A, in spite of the unfavourable *syn*-diaxial interaction between the axial *N*-methyl and C-9 methyl groups; the deshielding consequence of such an interaction is apparent from the lower field shift of the axial *N*-methyl resonance as compared with the axial *N*-methyl



A

(methiodide of 4.*4g*, partial formula)

of the α-salt (cf. axial *N*-methyl data for the isomeric 3-methyl derivatives of (4.7); α 47.3 ppm with equatorial 3-methyl, β 51.3 ppm with axial 3-methyl)[192].

The *N*-methyl shift data for 6,7-benzomorphans with C-3 (α-carbon) substituents is interpreted in terms of anticipated shielding effects at both *N*-methyls when the substituent is equatorial, and upfield shifts of equatorial *N*-methyl and downfield shifts for axial *N*-methyl when the substituent is axial. Thus, methiodide *N*-methyl shift data for the 3,5-dimethyl derivatives (3. *5*) and(3.*6*) (entries

25 and 26) confirm an equatorial orientation for 3-methyl in the α; both *N*-methyl resonances shielded in comparison with model values, and an axial placement in the β-isomer, equatorial *N*-methyl deshielded relative to the standard. The *N*-methyl shifts of the latter isomer are close to those of the methiodides of the 3-substituted 5,9-dimethyl derivatives 3.*38* and 3.*40* (entries 27 and 28), also assigned axial carbon substituents at C-3, CH_3 and CH_2Ph, respectively. Other ^{13}C n.m.r. features diagnostic of stereochemistry in benzomorphan bases, such as the relative α/β C-1, C-5, C-8 and C-3' shift of the isomers (3.5) and (3.6), are also apparent in the methiodide spectra.

Substituent effects of α-methyl groups on *N*-methyl proton shifts are qualitatively similar to those on corresponding ^{13}C resonances[204], and proton chemical shift data for the quaternary salts studied in this work corroborate the conclusions of configuration based on ^{13}C n.m.r. spectra. (Table 12). Taking the *N*-methyl resonances of α and β-metazocine as standards (Table 12, entries 1 and 2), shielding effects are found for both *N*-methyl signals of the α-3,5-dimethyl derivative 3.5 (Table 12, entry 3) in accord with its equatorial 3-methyl substituent, while shielding at equatorial *N*-methyl and deshielding at axial *N*-methyl is apparent for the axial 3-methyl derivatives (3.6 and 3.*38*; Table 12, entries 4 and 5). The *N*-methyl assignments of 3.*40* (Table 12, entry 6), made on the basis of the axial *N*-methyl shifts of (3.6 and 3.*38*) show that the axial 3-benzyl substituent has a marked deshielding influence on the equatorial *N*-methyl group, which was shown by the use of models to lie close to the aromatic plane of the benzyl group in the preferred conformation of the molecule. Chemical shift differences between isomeric

Table 12. ^{1}H chemical shifts of methiodides of some 6,7-benzomorphan derivatives; in DMSO-d_6 [a]

Entry	Compound [b]	eq-*N*-Me	ax-*N*-Me	3-Me	5-Me	9-Me
1	4.*4c*(α)	3.35	3.23	-	1.38	0.83
2	4.*4g*(β) [c]	3.32	3.20	-	1.30	1.38
3	3.*5*(α)	3.26	3.15	1.14	1.44	-
4	3.*6*(β)	3.22	3.44	0.63	1.43	-
5	3.*38*	3.26	3.42	0.64	1.38	0.84
6	3.*40*	(3.58)	(3.46)	-	1.31	0.84

a) Values in ppm from TMS; shifts in parentheses may be interchanged

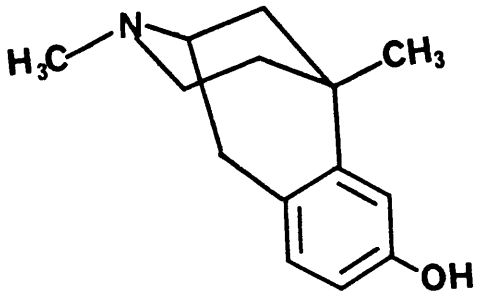
b) Base from which methiodide salt is derived

c) Previous data of $^{+}$N Me shifts in error (Ref. 151)

C-methyl resonances are of the same kind as those described for corresponding bases. For example, the α/β-9-methyl resonances of the metazocines (4.*4c* and 4.*4g*) and the 3-methyl resonances of (3.*5*) and (3.*6*).

2'-hydroxy-6,7-benzomorphans

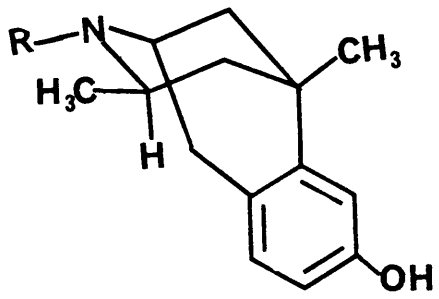
The assignment of the ^{13}C chemical shifts of 2,5-dimethyl-6,7-benzomorphan (3.*45*) (Table 13, entry 1) was accomplished by comparison with the model compound (4.*4b*) (Table 11, entry 1). The slight downfield shift at C-3 (about 4.2 ppm) is a result of the β-effect of *N*-methyl group, which also caused an upfield shift at C-8 by its



(3.45)

γ-shielding effect. The observed upfield shifts at C-5 and C-9, is due to the loss of α and β deshielding effects of C-9 methyl group as in (4.4b).

The 2'alkyl-3,5-dimethyl benzomorphan derivatives are considered next. Clear evidence of the equatorial orientation of the C-3 methyl group in (3.47) are its ^{1}H chemical shift at 0.93 ppm (Table 8, entry 2) and ^{13}C shift at 20.53 ppm (Table 13, entry 2),values comparable to similar shifts in the non-phenolic analogue (3.5; Table 11, entry 8).



(3.47) R = Me

(3.49) R = H

(3.50) R = $-CH_2CH=CH_2$

(3.51) R = $-CH_2-C-C_3H_5$

Table 13. ^{13}C chemical shifts of some 2'-OH-6,7-benzomorphan derivatives in DMSO[a]

Entry	Compound	C-1	C-3	C-4	C-5	C-2'[b]	C-8	C-9	N-$\underline{C}H_3$	C-3'	C-4'	C-5'	C-9'
1	3.*45*	52.55	46.86	40.31	31.42	155.10	26.00	39.43	42.31	-	-	28.95	-
2	3.*49*	54.82	50.00	49.79	32.94	155.16	26.87	39.44	39.93	20.53	-	27.95	-
3	3.*47*	46.64	43.56	49.24	32.94	155.21	36.57	38.95	-	22.27	-	28.33	-
4	3.*50*	50.17	48.87	50.60	32.82	155.32	27.57	39.71	c	21.02	-	28.01	-
5	3.*51*	49.52	48.65	50.59	32.72	155.21	27.41	39.65	d	20.69	-	28.08	-
6	3.*54*	52.65	54.66	(42.15)	34.67	154.01	26.00	(41.01)	39.87	-	13.27	25.30	-

a). Bases in DMSO-d_6 unless otherwise stated; chemical shifts in ppm from TMS, shifts in parentheses may be interchanged

b). Aromatic carbon resonances fell in the range 147 - 112 ppm.

c). N-$\underline{C}H_2$-$\underline{C}H$=$\underline{C}H_2$ resonances at 52.67, 138.04 and 115.38 ppm respectively.

d). N-$\underline{C}H_2$-$\underline{C}\equiv H$ resoannces at 53.52, 9.97, 2.60 and 5.90 ppm respectively.

The *N*-desmethyl analogue (3.*49*) showed an expected upfield shift at C-1 and C-3, with a downfield shift at C-8, the former due to the loss of β-effect at C-1 and C-3, and the latter due to the loss of the γ-effect of the *N*-methyl group. Other *N*-alkyl analogues (3.*50*) and (3.*51*) are distinguished by the ^{13}C shifts of the *N*-substituents (Table 13, entries 4 and 5) and a slight upfield shift at C-3 due to additional γ-effect at that position compared to the *N*-methyl compound. The non-equivalence of the methylene carbons of the cyclopropyl group in (3.*51*; Table 13, entry 5), evident from the separate ^{13}C shifts, is probably due to the disruption of symmetry of the methylene carbons by a gauche effect of the 3-methyl.

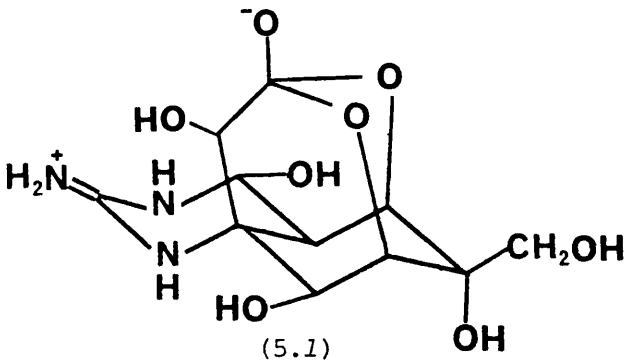
The last series of compounds to be considered are the 2-methyl-4,5-dialkyl benzomorphans. Synthesis of 2,4,5-trimethyl-6,7-benzomorphan gave one-isomer (3.*54*) judged to have an equatorial methyl group at C-4 by its ^{1}H n.m.r. doublet at 0.57 ppm (a value comparable to that of the non-phenolic derivative prepared by Parfitt and Walter)[129]. In the ^{13}C n.m.r. spectrum, the lack of an appreciable γ-effect at C-9, expected of a C-4 axial methyl (similar to that shown by axial C-9 methyl isomer at C-4, Table 11, entry 6), along with a downfield shift at C-3 characteristic of an equatorial methyl group, lent support to this assignment. Lastly, the *N*-Me ^{13}C shift in (3.*54*) is slightly upfield of that in (3.*45*) as a result of the γ-effect of an equatorial 4-methyl group.

CHAPTER 5

2-Amidino-6,7-Benzomorphans as Potential Analgesics

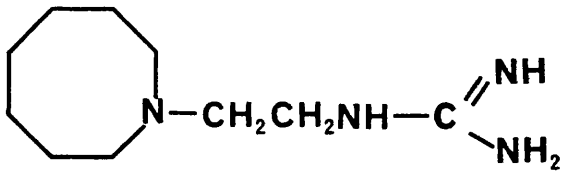
5.1 Introduction

The interest in guanidine derivatives stems principally from the discovery of high biological potency in a number of natural and synthetic agents possessing the group either in the free or cyclic form. Tetrodotoxin (5.*1*) and saxitoxin are examples of animal and natural products that elicit a dramatic blocking of axon transmission in mammals through blockade of the passive entry of sodium ions[206].



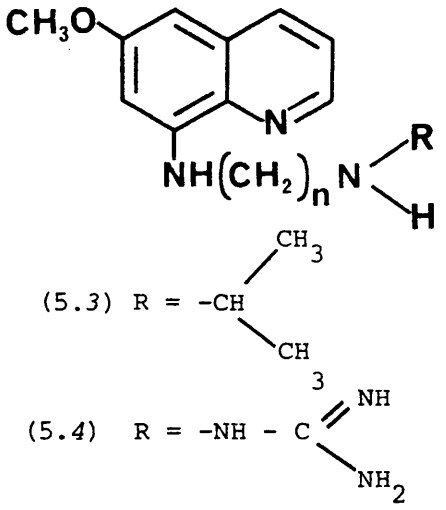
(5.*1*)

The former may be isolated from the ovaries of the Japanese goldfish and the Pacific blue ring octopus, whereas the latter is a seasonal algal toxin ingested by shellfish. A notable synthetic guanidine is the hypotensive agent guanethidine (5.*2*) an adrenergic neuron blocking agent[207].



(5.*2*)

A number of guanidine derivatives have been investigated not only for their effects on the cardiovascular system, but also as potential oral hypoglycaemic[208] and also as chemotherapeutic agents[209]. An example of the latter is seen with the replacement of the terminal amino group of the side chain of the 8-aminoquinoline antimalarials (5.*3*) by an N'-guanidino moiety in the investigation[209] of the effect of a change in the character of the side chain on toxicity. The N'-guanidino compounds (5.*4*; n = 2 - 5) were found to be of lower toxicity.



(5.*3*) R = -CH(CH$_3$)CH$_2$CH$_2$CH$_3$

(5.*4*) R = -NH - C(=NH)NH$_2$

In opiate-receptor interactions, the amine nitrogen and the lone electron pair have been proposed as being important for their activities, either by considering the active species as the protonated amine[42, 182], or as the free amine[180,181]. If this is so, then the preparation of 2-amidino-6,7-benzomorphans (which are substituted guanidines) may shed light on the following:

a) whether an increase in the basic strength and size of the basic centre (amidines and guanidines are stronger bases than amines), affects analgesic activity;

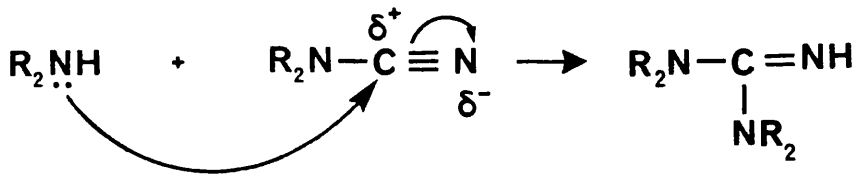
and b) whether moving the charge centre from piperidine ring nitrogen to carbon affects activity, since infra-red studies and molecular orbital calculations have shown the positive charge in the guanidinium ion to be located in the vicinity of the central carbon atom[210].

The preparation and pharmacological evaluation of 2-(N'-alkyl and aryl amidino)-5,9-dimethyl-6,7-benzomorphan has been attempted and is discussed below.

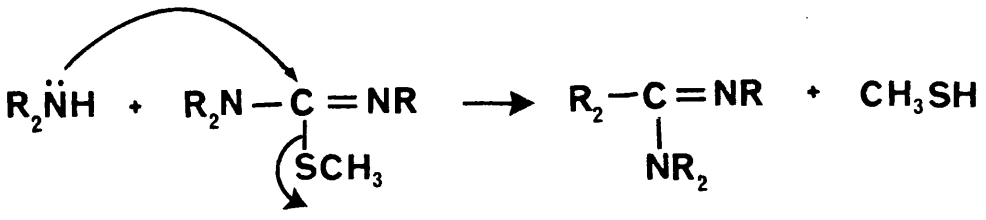
5.2 Discussion

Two synthetic routes to guanidines are in common use.

a) the addition of amines to cyanamides[211-213]

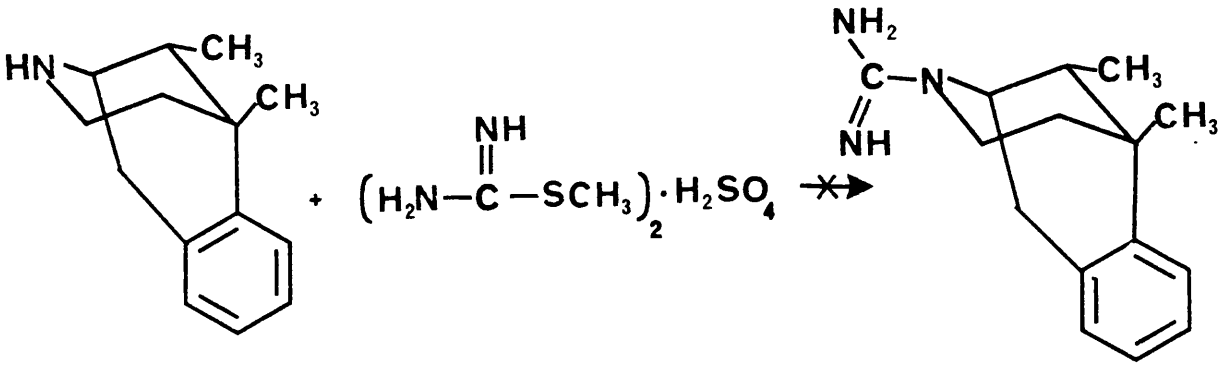


b) the displacement of an alkyl mercaptan by an amine from an alkylisothiouronium salt[212,213]



A study of the scope of the latter reaction by Short and Darby revealed that primary amines are generally more reactive than secondary amines, though there are exceptions[214].

The reaction of 5,9-dimethyl-6,7-norbenzomorphan with *S*-methyl-isothiouronium sulphate in aqueous ethanol was chosen for the preparation of 2-amidino-5,9-dimethyl-6,7-benzomorphan (5.*6*).



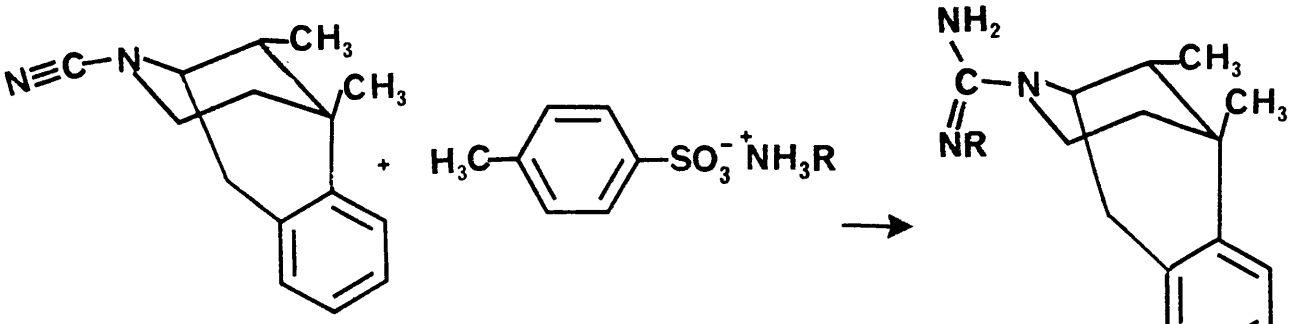
(5.*5*)

(5.*6*)

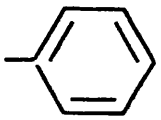
However, in all reactions attempted, only starting material was recovered. Although it has been demonstrated that 1^{o} amines are generally more reactive than 2^{o} amines it was considered that changes of reaction conditions, for example, solvent, reaction time and proportion of the reactants may afford results.

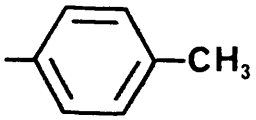
The 2-(N'-arylamidino)-5,9-dimethyl-6,7-benzomorphan were obtained by heating 2-cyano-5,9-dimethyl-6,7-benzomorphan and appropriate anilinium *p*-toluene sulphonate in refluxing toluene, with a trace of pyridine (Scheme 18).

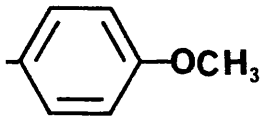
SCHEME 18



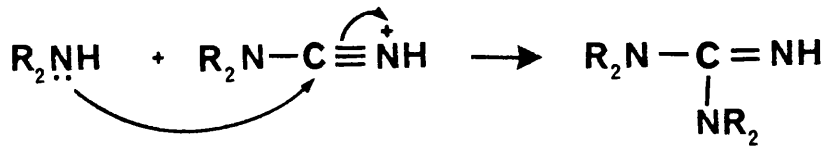
(5.7)

(5.8) R = 

(5.9) R = 

(5.10) R= 

The products were purified by silica gel column chromatography, and identified by ^{1}H, ^{13}C n.m.r. and i.r. characteristics. However, attempts to employ the *p*-toluene sulphonate salt of aliphatic amines such as ethylamine and butylamine were unsuccessful. An insight into the failure of aliphatic amines to react can be gained by considering the mechanism of the reaction involved. Odo[211] reported that the mechanism involved a reversible nucleophilic attack of the free amine on the protonated cyanamide. Consequently, the availability of the nitrogen lone electron pair in the amine dictates the ease of reaction. Aniline and other aryl



amines are weaker bases than, for example, ethylamine. Therefore, the *p*-toluene sulphonate salts of anilines will be stronger acids than those derived from ethylamine and other aliphatic amines. So, under the reaction conditions, the arylamines will exist more readily as the free amine than will the alkylamines. Secondly, the catalysing species (H^+) will be easily neutralised by stronger alkylamines compared with the arylamines and therefore, provides no driving force for the reaction to occur. A combination of these two factors will facilitate the reaction of the arylamines whilst retarding those of the alkylamines, as observed.

The ^1H n.m.r. spectra of the 2-amidino benzomorphans were similar (Table 14) and provide no means of identification except that the Ar-$C\underline{H}_3$ shift of (5.*9*) at 2.28 ppm and Ar-$OC\underline{H}_3$ ^1H n.m.r. shift of (5.*10*) at 3.75 ppm.

However, identification was possible from the ^{13}C n.m.r. shift data of the compounds prepared (Table 15). Conversion of 2-cyano-5,9-dimethyl-6,7-benzomorphan to the 2-(N'-phenylamidino)-analogue (5.*8*) was confirmed by the downfield ^{13}C n.m.r. shift of the 2-cyano

Table 15. ^{13}C Chemical shifts of the aryl portion of the 2-substituents of some 2-(arylamidino)-5,9-dimethyl-6,7-benzomorphan in $CDCl_3$ [a]

Compound	C-1"	C-3"	C-4"	C=NH	4"-R
5.7	-	-	-	(b)	-
5.8	150.61	123.24	121.68	152.07	
5.9	147.84	122.98	130.83	152.18	Ar-$\underline{C}H_3$ 20.75
5.10	143.72	114.85	154.94	152.61	Ar-O$\underline{C}H_3$ 55.53

a) Values in ppm from TMS

b) 2-$\underline{C}\equiv N$ carbon resonance 118.32 ppm

Table 14. ^{1}H n.m.r. shifts of 2-cyano and some 2-(arylamidino)-5,9-dimethyl-6,7-benzomorphans in $CDCl_3$[a].

Compound	5-Me	9-Me	4"-R	NH
5.7	1.43	0.87 (d) J=6Hz	-	-
5.8	1.40	0.87 (d)		3.92
5.9	1.40	0.88 (d)	Ar-CH_3 2.28(s)	3.92
5.10	1.40	0.88 (d)	Ar-OCH_3 3.75(s)	3.92

a) Values in ppm from TMS.

carbon in (5.7) from 118.32 ppm to 152.07 ppm, indicating the presence of $\diagdown$C=NH. Both the 2-(*p*-tolylamidino) and 2-(*p*-anisylamidino) derivatives showed a $\diagdown$C=NH carbon shift near 152 ppm (Fig. 6). The shifts of other aromatic carbons in the molecule provide the evidence for the presence of the amidino aromatic ring, and also serve to distinguish the various compounds themselves. Thus, a downfield shift of the aromatic α-carbon (C-4") caused by the 4"-CH_3 and 4"-OCH_3 groups is observed, as well as shielding effects at the *ortho* and *para* carbons (C-3" and C-1") (Fig. 6). Compounds (5.9) and (5.10) were submitted for pharmacological evaluation.

Pharmacology

Data from the pharmacological evaluation of (5.9) and (5.10) are awaited but the 2-(N'-phenylamidino)-6,7-benzomorphan hydrochloride

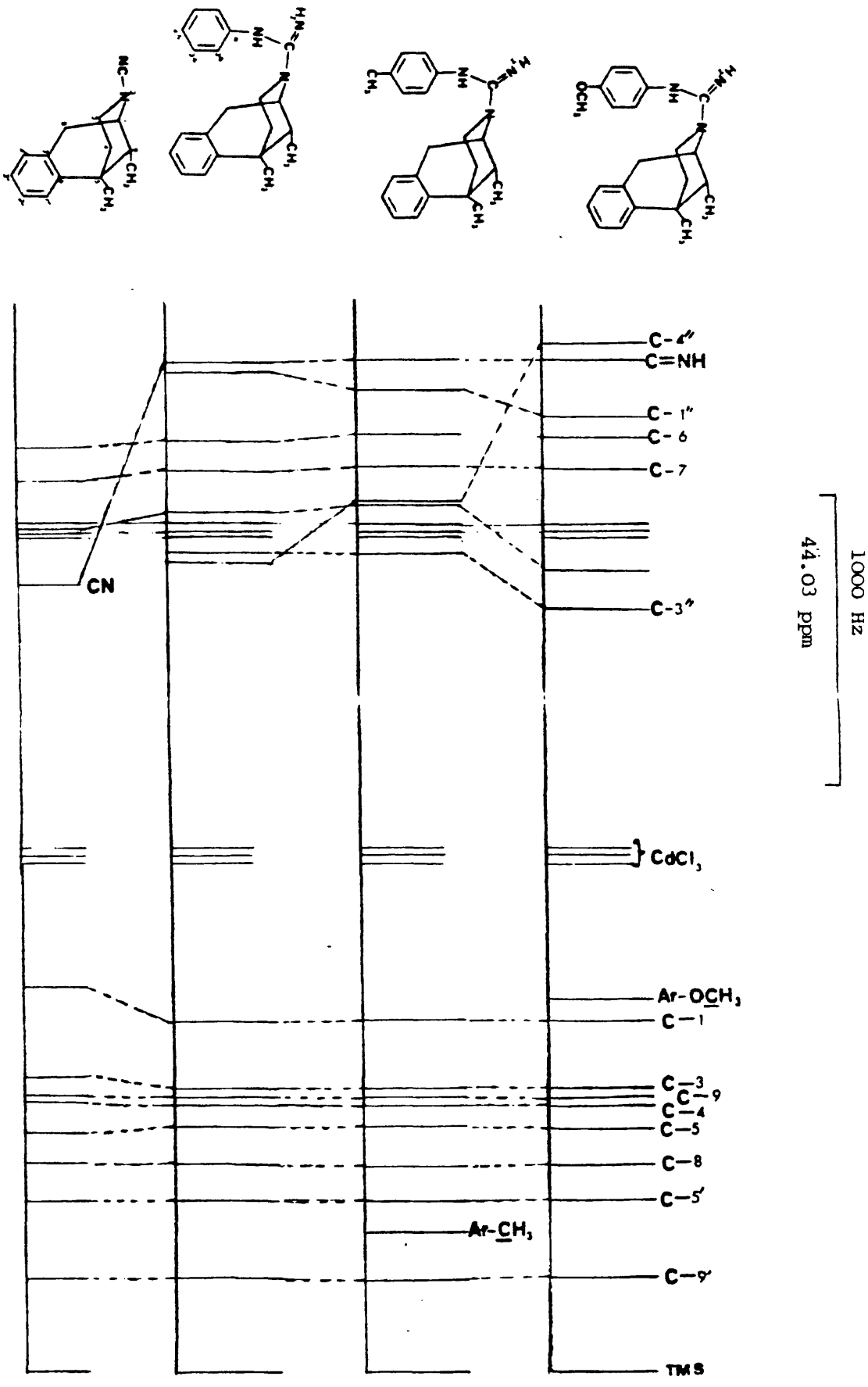
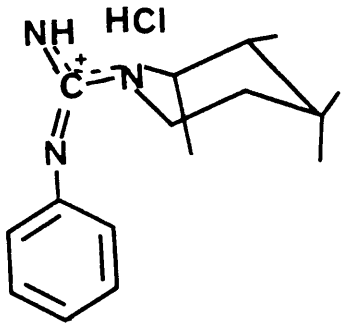
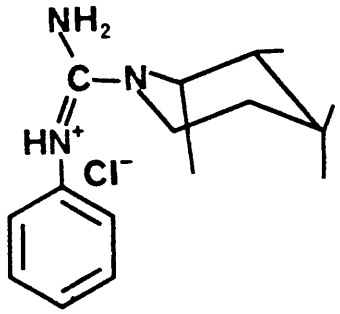


Fig. 6. Correlation diagram of ^{13}C n.m.r. chemical shifts of 2-cyano and some 2-(arylamidino)-5,9-dimethyl-6,7-benzomorphans.

(5.*8*) proved to be without analgesic activity. It is worthwhile to note that the N'-aryl amidino derivatives prepared as a result of synthetic difficulties with the N'-alkylamidino analogues, are weaker bases, and secondly, they might not have a symmetrical charge distribution in the cation. Thus, if the positively charged nitrogen centre is the pivot on which analgesics bind first to the receptor as suggested by Portoghese[43b], then a shift of this centre as in (5.*8a*) or (5.*8b*) will displace the other substituents in the molecule from their productive binding positions, thereby leading to loss of activity.



(5.*8a*)



(5.*8b*)

Secondly,[215,216] it is reported that guanidinium ions bind less strongly to carboxylate ions of proteins than ammonium ions. If a similar phenomenon applies at the opiate receptor, a less productive binding and hence,low activity might result. In conclusion, it is hoped that the preparation and evaluation of unsubstituted 2-amidino-5,9-dimethyl-6,7-benzomorphan and some other alkyl analogues, will afford data that could lead to a definitive conclusion.

PART III

EXPERIMENTAL

All melting points (uncorrected) were determined on a Townson and Mercer melting apparatus. The infra-red spectra (liquids as films, solids as KBr discs or Nujol mulls) were recorded on a Unicam SP 1025 spectrophotometer.

Routine 60 mHz ^{1}H n.m.r spectra were recorded on a Perkin-Elmer R12B and JEOL JNM-PMX 60SI n.m.r. spectrometers, 100 mHz spectra on a JEOL PS 100, and the one 220 mHz spectrum (p.121) was recorded by the Physicochemical Measurement Unit (PCMU), Harwell.

Proton and off-resonance decoupled ^{13}C spectra were obtained from a JEOL FX 90Q n.m.r. spectrometer operating at 22.5 kHz. Samples were prepared in 5 mm o.d. tubes as approximately 10% solutions in $CDCl_3$ with 2% $SiMe_4$ as reference. The deuterium of the solvent provided the lock signal. Spectra were recorded with 8K data points; the probe temperature was 23°C. For an average spectral width of 5000 Hz, a 4s pulse corresponding to a tilt angle of 30° was employed with a 1.8192s interval between pulses.

Mass spectra were measured on a VG Micromass 7070 E mass spectrometer operating at 70 eV (EI), and with Xe/Glycerol for fast atom bombardment (FAB).

Elemental analysis were carried out by the microanalysis section of the School of Pharmacy, Brunswick Square, University of London.

Dried solvents were distilled from lime and stored over type

4A molecular sieves, or were dehydrated with freshly pressed sodium wire. Distillation under pressure was carried out in a Büchi GKR-50 glass tube oven.

2,3,5-Trimethyl-6,7-benzomorphan (3.5 and 3.6)

The method employed was that of Parfitt and Walters[129].

An ice-cold stirred suspension of 2,4-lutidine methiodide (75 g) in dried ether (100 ml) was treated with about 400 ml of ethereal benzyl magnesium and benzyl chloride 75 ml). The mixture was stirred vigorously for 2 hr in the cold and then added to a mixture of 60% perchloric acid (150 ml) and crushed ice (500 g) to give a three phase mixture. The product which precipitated in the centre layer was collected after 30 min and washed with ethanol to give, after drying, 81.06 g (86%) of 2-benzyl-1,4,6-trimethyl-1,2-dihydropyridine perchlorate. This product was suspended in a mixture of methanol (250 ml) and 2 N NaOH (350 ml), and treated with sodium borohydride (14.0 g) during 15 min. The mixture was kept at 55 - 60°C for 1½ hr and then diluted with water 200 ml, cooled and extracted with ether (5 x 200 ml). The combined ether extract (Na_2SO_4 dried) was evaporated *in vacuo* to give 44.11 g of the tetrahydro product, which, with 47% aqueous HBr (123 ml) and 45% HBr in acetic acid (74 ml), was refluxed for 48 hr. The resultant solution was poured into ice-water, made alkaline with ammonia and extracted with ether (4 x 100 ml). The ether solution was extracted with 2 N HCl (3 x 100 ml), and the combined acid solution was basified with aqueous ammonia. Extraction with ether (4 x 100 ml) followed by drying and evaporation of the ether *in vacuo* gave 40.60 g (92%) of the crude benzomorphan as an oil. Distillation over a short path at

130°C/0.5 mm Hg gave 34.57 g of pure base. The major isomer (3.5) was separated as the hydrochloride and the *minor isomer* (3.6) as the oxalate. Both the hydrochloride and methiodide salts of both isomers were prepared and recrystallised from ethanol-ether mixture.

(3.5) HCl m.p. 152 - 154°C

(3.5) methiodide m.p. 268 - 269°C (Lit.[129] 264 - 265.5°C, from ethanol).

Anal. calcd. for $C_{16}H_{24}NI$ requires C, 53.78; H, 6.77; N, 3.92%:

Found: C, 53.99; H, 7.09; N, 3.79%

(3.6) HCl m.p. 222 - 224°C

(3.6) methiodide m.p. 242 - 243°C

Anal. calcd. for $C_{16}H_{24}NI$ requires

C, 53.78; H, 6.77; N, 3.92%:

Found: C, 53.66; H, 6.96: N, 3.84%.

cis-2,5,9-Trimethyl-6,7-benzomorphan (3.*11*)

2,5,9-Trimethyl-6,7-benzomorphan was prepared by the method described for 2,3,5-trimethyl-6,7-benzomorphans (3.5 and 3.6). The perchlorate from the reaction of benzyl magnesium chloride with 3,4-lutidine methiodide (100 g) was separated into the chloroform soluble and insoluble portions. The chloroform insoluble portion was reduced with sodium borohydride and the tetrahydro product cyclised to give an oil which after distillation at 140°C/2 mm Hg gave 29.5 g of *cis*-2,5,9-trimethyl-6,7-benzomorphan, as shown

by the ^{1}H and ^{13}C n.m.r. spectra of the product.

$\Delta^{3,4}$-Dehydro-2,3,5-trimethyl-6,7-benzomorphan (as the iminium perchlorate 3.*17*)

Mercuric oxide (52.40 g; 240 m Mol) was added, gradually, over 15 min, to a stirred solution of 2,3,5-trimethyl-6,7-benzomorphan (3.5; 10.42 g, 50 mMol) in 40% acetic acid (200 ml) heated under reflux. The mixture was refluxed for 2 hr, cooled and the precipitated mercurous acetate collected and washed with 5% acetic acid solution (50 ml). The combined filtrate and washings were saturated with H_2S and the resultant suspension filtered through celite. After basification with potassium carbonate the filtrate was extracted with chloroform (5 x 200 ml). The chloroform extract was acidified with ether previously saturated with perchloric acid and the solvent removed to give the *product* as a solid (7.59 g; 50%). Recrystallisation from ethanol gave colourless crystals, m.p. 164 - 166°C.

(3.5 and 3.*6*) gave identical product.

ν_{max} (Nujol): 1680 cm^{-1} ($\diagdown\!\!\diagup C = \overset{+}{N}$)

Anal. calcd. for $C_{15}H_{20}NO_4Cl$ requires

C, 57.4; H, 6.4; N, 4.7%:

Found: C, 56.9 ; H, 6.4; N, 4.7%.

EI/MS M^+ 213 FAB/MS $(M + 1)^+$ 214

3-Cyano-2,3,5-trimethyl-6,7-benzomorphan (3.26)

METHOD A

To a solution of potassium cyanide (1.20 g; 18.0 mMol) in water (50 ml) in a separatory funnel, was added the iminium perchlorate (2.0 g; 60 mMol). The mixture was layered with ether (50 ml) and shaken vigorously. The ether layer was separated and a further extraction with ether (3 x 100 ml) undertaken. The combined ether extract was dried and concentrated to give the *product* as an oil (1.05 g; 73%) which crystallised on standing. The base was recrystallised from petroleum spirit (60 - 80°C) and had a m.p. 102 - 104°C.

ν_{max} (Nujol): 2220 cm^{-1} (-C≡N)

Anal. calcd. for $C_{16}H_{20}N_2$ requires

C, 79.9; H, 8.4; N, 11.7%.

Found: C, 79.9; H, 8.6; N, 11.8%.

METHOD B

The method employed was that of Groutas *et al.*[165].

To a solution of 2,3,5-trimethyl-6,7-benzomorphan (3.5; 10.50 g, 49.0 mMol) in methanol (50 ml) was added 30% hydrogen peroxide (30 ml.)The mixture was stirred for 48 hr and then heated under reflux for 5 hr. Palladium/charcoal (0.30 g) was added to the stirred, cooled solution (0°), and stirring was continued for 1 hr. The catalyst was removed, the filtrate evaporated to small volume and dichloromethane (100 ml) added. The solution was dried over anhydrous Na_2SO_4 and evaporated to give a solid (9.3 g). This was dissolved in dichloromethane

(100 ml), cooled to 0°C and trifluoroacetic anhydride (36 ml) added, with stirring. After 1 hr, the mixture was heated at 50°C for 20 min and then evaporated to give an oil. A solution of potassium cyanide (54 g) in water (100 ml) was added to the resultant oil, at 0°, and the mixture stirred at room temperature for 1 hr. The mixture was extracted with ether (3 x 100 ml). The ethereal extracts were dried ($MgSO_4$) and evaporated to give the *product* as an oil (7.80 g; 66%) which crystallised on standing. Recrystallisation of the base from petroleum spirit (60 - 80°C) gave a light yellow solid, m.p. 102 - 104°C. ^1H and ^{13}C n.m.r. data were identical with that of the product by method A.

2-Cyanomethyl-3,5-dimethyl-6,7-benzomorphan (3.29)

By the method B described for (3.5) above, 2,3,5-trimethyl-6,7-benzomorphan (3.6; 14.50 g; 69.6 mMol) gave the titled *product* as an oil (13.48 g; 80%) which crystallised on standing. Recrystallisation from n-hexane gave colourless plates, m.p. 68 - 70°C.

ν_{max} (Nujol): 2225 cm^{-1} (-C≡N)

Anal. calcd. for $C_{16}H_{20}N_2$ requires

C, 79.9; H, 8.4; N, 11.6:.

Found: C, 79.8; H, 8.5; N, 11.6%.

2-Aminoethyl-3,5-dimethyl-6,7-benzomorphan (3.30)

To a cooled and stirred suspension of $LiAlH_4$ (0.16 g) in anhydrous ether (20 ml), was added a solution of 2-cyanomethyl-3,5-dimethyl-6,7-benzomorphan (0.5 g; 2.1 mMol) in ether (20 ml).

The reaction was left stirring for 1 hr. at room temperature. The excess $LiAlH_4$ was destroyed by addition of H_2O (0.16 ml), followed by 5 N NaOH (0.12 ml) and finally H_2O (0.48 ml)[205]. The filtrate obtained after removing the precipitate was concentrated *in vacuo* to give the *product* as an oil (0.47 g; 92%), which was converted to the *oxalate salt*. Recrystallisation from ethanol gave colourless crystals, m.p. 190 - 192°C.

Anal. calcd. for $C_{20}H_{28}N_2O_8.H_2O$ requires

C, 54.3; H, 6.8; N, 5.9%

Found: C, 53.9; H, 6.8; N, 6.3%.

Similar reduction of 3-cyano-2,3,5-trimethyl-6,7-benzomorphan (3.*26*) afforded an equal mixture of *cis* and *trans*-2,3,5-trimethyl-6,7-benzomorphans (3.5) and (3.6), as shown by the ^1H and ^{13}C n.m.r. spectra of the product.

3-Cyano-2,5,9-trimethyl-6,7-benzomorphan (3.*36*)

By the method B described for cyanation of (3.5) above, 2,5,9-trimehtyl-6,7-benzomorphan (3.*11*; 15.12 g, 69.5 mMol) gave the *product* as an oil (13.20 g; 78%) which crystallised on standing. The crude product was chromatographed on a column of silica gel (200 g) and eluted with chloroform. Fractions were collected in 30 ml portions. The pure fraction was concentrated *in vacuo* and the base which crystallised out, was recrystallised from n-hexane to give colourless crystals, m.p. 100 - 101°C.

ν_{max} (film): 2220 cm^{-1} (-C≡N)

Anal. calcd. for $C_{16}H_{20}N_2$ requires

C, 79.95; H, 8.38; N, 11.65%:

Found: C, 79.62; H, 8.45; N, 11.84%.

3-Aminomethyl-2,5,9-trimethyl-6,7-benzomorphan (3.37)

To a cooled and stirred suspension of $LiAlH_4$ (0.50 g) in anhydrous ether (25 ml) was added a solution of 3-cyano-2,5,9-trimethyl-6,7-benzomorphan (1.50 g; 6.25 mMol) in ether (25 ml).

The reaction was refluxed gently for 1 hr, after which the excess $LiAlH_4$ was destroyed with H_2O (0.5 ml), followed by 5 N NaOH (0.33 ml) and finally H_2O (1.5 ml). The filtrate obtained after removing the precipitate was concentrated *in vacuo* to give the *product* as an oil (1.35 g; 78%), which was converted to the *oxalate* and recrystallised from methanol, m.p. 165 - 168°C.

Anal. calcd. for $C_{20}H_{28}N_2O_8.\frac{1}{2}H_2O$ requires

C , 55.42; H, 6.74; N, 6.46%:

Found: C, 55.02; H, 7.16; N, 6.65%.

Preparation of 3-alkyl-6,7-benzomorphans

The following are generalised procedures.

METHOD A

To a cooled and stirred suspension of the iminium perchlorate (3.17) in anhydrous ether was added the appropriate Grignard reagent solution, dropwise. The reaction mixture was stirred in the cold for 3 hrs, poured into ice-water and basified

with ammonia. The solution was extracted with ether (3 x 100 ml), dried (Na_2SO_4) and concentrated *in vacuo* to give the product.

METHOD B

To a cooled and stirred ethereal solution of the appropriate Grignard reagent or alkyllithium was added, dropwise, a dilute solution of 3-cyano compound in anhydrous ether. The reaction was stirred for 3 hr (for 3-cyano-2,3,5-trimethyl-6,7-benzomorphan) and overnight (for 3-cyano-2,5,9-trimethyl-6,7-benzomorphan), after which the reaction mixture was poured into ice-cold water. The ether layer was separated and the aqueous portion was extracted further with ether(3 x 100 ml). The combined ether extract was dried (Na_2SO_4) and concentrated *in vacuo* to give the product.

3-Benzyl-2,3,5-trimethyl-6,7-benzomorphan (3.*32*)

By method A (2.50 g; 8 mMol) of iminium perchlorate (3.*17*) gave the crude *product* as an oil (2.89 g). Short path distillation at 170°C/0.5 mm Hg gave pure base (2.19 g; 90%).
The *hydrochloride* separated as colourless plates from ethanol-ether mixture and had m.p. 246 - 249°C.

Anal. calcd. for $C_{22}H_{28}NCl$ requires

C, 77.28; H, 8.25; N, 4.10%:

Found: C, 77.48; H, 8.53; N, 4.10%.

Both the ^{1}H and ^{13}C spectra of the product obtained by method B were identical with those of the product by method A.

3-Allyl-2,3,5-trimethyl-6,7-benzomorphan (3.*33* and 3.*34*)

By method A (3.0 g; 9.5 mMol) of iminium perchlorate (3.*17*) gave the *product* as an oil (1.78 g, 73%), after distillation of the crude product at 150°C/ 1 mm Hg. A TLC examination of the oil showed two major spots corresponding to the two isomers. The oil was chromatographed on a column of silica gel (60 g) and eluted with 100% chloroform, and 10%, 25%, 50% ethyl acetate in chloroform respectively. Fractions were collected in 30 ml portions. The pure minor isomer was contained in the 100% chloroform and 10% ethylacetate in chloroform fractions and, the major isomer in 25% ethyl acetate in chloroform fraction. The pure isomers were converted to the hydrochloride salts. The hydrochlorides separated as colourless crystals from ethanol-ether mixture.

(3.*33*) HCl had a m.p. 246 - 247°C

Anal. calcd. for $C_{18}H_{26}NCl$ requires

C, 74.07; H, 8.98; N, 4.80%:

Found: C, 73.90; H, 9.06; N, 4.84%.

(3.*34*) HCl had a m.p. 252 - 253°C.

Anal. calcd. for $C_{18}H_{26}NCl$ requires

C, 74.07, H. 8.98; N, 4.80%:

Found: C, 73.80; H, 9.17; N, 4.84%.

The isomers from the product obtained by method B had the same ^{1}H and ^{13}C n.m.r. characteristics as those by method A.

2,3,5,9-Tetramethyl-6,7-benzomorphan (3.*38*)

By method B (2.50 g; 10 mMol) of 3-cyano-2,5,9-trimethyl-6,7-benzomorphan gave the *product* as an oil (1.20 g; 50%), after short path distillation of the crude at 150°C/0.2 mm Hg.

The *hydrochloride* separated as colourless crystals from ethanol-ether mixture, and had m.p. 268 - 270°C.

Anal. calcd. for $C_{16}H_{24}NCl$ requires

C, 72.29; H, 9.10; N, 5.27%:

Found: C, 72.43; H, 9.11; N, 5.17%.

The *methiodide* separated as plates from ethanol and had m.p. 240 - 241°C.

Anal. calcd. for $C_{17}H_{26}NI$ requires

C, 54.99; H, 7.06%:

Found: C, 55.17; H, 7.13%.

3-Ethyl-2,5,9-trimethyl-6,7-benzomorphan (3.*39*)

By method B (3.0 g; 12.5 mMol) of 3-cyano-2,5,9-trimethyl-6,7-benzomorphan gave the *product* as an oil (1.40 g; 46%), after distillation of the crude product at 130°C/0.5 mm Hg.

The *hydrochloride* separated from ethanol-ether mixture as colourless crystals, and had m.p. 271 - 273°C.

Anal. calcd. for $C_{17}H_{26}NCl$ requires

C, 72.96; H, 9.37; N, 5.01%:

Found: C, 72.59; H, 9.49; N, 5.04%.

3-Benzyl-2,5,9-trimethyl-6,7-benzomorphan (3.*40*)

By method B (3.0 g; 12.5 mMol) of 3-cyano-2,5,9-trimethyl-6,7-benzomorphan gave the *product* as an oil (1.81 g, 48%), after distillation at 170°C/0.2 mm Hg. A TLC analysis of the oil showed two isomers. Attempts to separate the two isomers on a silica gel column resulted in the isolation of one isomer (major) in all cases tried.

The *hydrochloride* separated as colourless crystals from ethanol-ether mixture and had m.p. 217 - 219°C.

Anal. calcd. for $C_{22}H_{28}NCl$ requires

C, 77.28; H, 8.25; N, 4.10%:

Found: C, 76.93; H, 8.52; N, 4.09%.

The *methiodide* separated as tiny needles from ethanol and had m.p. 247 - 249°C.

Anal. calcd. for $C_{23}H_{30}NI$ requires

C, 61.75; H, 6.75%:

Found: C, 62.21; H, 6.54%.

3-Phenethyl-2,5,9-trimethyl-6,7-benzomorphan (3.*41*).

By method B (3.0 g; 12.5 mMol) of 3-cyano-2,5,9-trimethyl-6,7-benzomorphan gave the *product* as an oil (1.46 g; 40%), after short path distillation of the crude product at 160°C/1 mm Hg.

The *hydrochloride* separated as fluffy needles from ethanol-ether mixture and had m.p. 236 - 238°C.

Anal. calcd. for $C_{23}H_{30}NCl.\frac{1}{2}H_2O$ requires

C, 75.70; H, 8.29; N, 3.84%:

Found: C, 75.77; H, 8.63; N, 3.38%.

N-Methylation of α-normetazocine

α-Normetazocine (1g), formic acid 98% (0.56 g) and 37% aqueous formaldehyde (0.17 g) were heated together on a steam bath for 3 hr. Aqueous ammonia solution was added to the cooled mixture which was then extracted with chloroform (3 x 50 ml). The bulked extracts were dried and evaporated to dryness to give α-metazocine as a solid (0.95;, 89%). Recrystallisation from ethanol gave colourless crystals, m.p. 230 - 232°C (Lit.[16,151] 231 - 233; 228 - 233°C).

Under the same conditions, β-normetazocine (0.5 g, 2.3 mMol) gave β-metazocine as a solid (0.40 g, 75%) which was recrystallised from ethanol, m.p. 211 - 213°C (Lit.[16,151] 220 - 221.5; 215 - 217.5°C).

Anal. calcd. for $C_{15}H_{21}NO$ requires

C, 77.88; H, 9.15; N, 6.05%:

Found: C, 77.45; H, 9.22; N, 5.84%.

α and β-Metazocine methiodides

The following is a general procedure:

The sample of benzomorphan (0.5 g) was dissolved in a minimum amount of acetone or methanol. Excess iodomethane was added, and

the solution thoroughly mixed. Ether was then added until the mixture was just about to be cloudy, and the mixture was left to crystallise out at room temperature. The solid which separated was recrystallised from methanol, ethanol or a mixture of ethanol and ether:

α-metazocine methiodide, m.p. 253-255°C (from ethanol

Anal. calcd. for $C_{16}H_{24}NOI$ requires

C, 51.48; H, 6.48%:

Found, C, 51.62; H, 6.46%.

β-metazocine methiodide, m.p. 238 - 240°C (from ethanol)

Anal. calcd. for $C_{16}H_{24}NOI$ requires

C, 51.48; H, 6.48; N, 3.75%:

Found: C, 51.04; H, 6.66; N, 3.50%.

4-Methoxybenzyl chloride

4-Methoxybenzyl alcohol (50 g) in ether (100 ml) was added dropwise to conc. HCl (70 ml) under ether (100 ml). After stirring for 45 min at room temperature the two layers were separated. The combined ether layer and ether washings (2 x 50 ml) of the aqueous layer were washed with saturated aqueous $NaHCO_3$ solution (2 x 100 ml) and then with 10% aqueous sodium carbonate solution (2 x 100 ml). The dried (Na_2SO_4) ether solution was evaporated to 55.0 g of crude material. Distillation over a short path at 120°C/0.3 mm Hg afforded the product as a clear, colourless oil (46.90 g; 88%), which was used immediately. The ^1H

and ^{13}C n.m.r. spectra of the product was consistent with the structure.

^{13}C n.m.r. spectra: $OCH_3C_6H_4\underline{\underline{C}}H_2OH$ 64.25 ppm

$\underline{\underline{C}}H_2Cl$ 46.20 ppm

4-Methoxybenzyl magnesium chloride

A mixture of magnesium powder (15 g) and magnesium turnings (3 g) was vigorously stirred under refluxing anhydrous ether (500 ml). 4-Methoxybenzyl chloride (46.9 g) in anhydrous ether (250 ml) was added dropwise over a 1 hr interval and the reaction was left stirring for an additional 1 hr. The resulting Grignard reagent was filtered through glass cotton to remove the finely divided magnesium powder and then used in the next experiment.

2'-Hydroxy-2,3,5-trimethyl-6,7-benzomorphan (3.47)

A stirred suspension of 2,4-lutidine methiodide (25 g; 0.1 mole) in anhydrous ether was treated with ethereal *p*-methoxybenzyl magnesium chloride from above. The mixture was stirred for 2 hr at room temperature and then added with vigorous stirring to a mixture of 60% perchloric acid (60 ml) and crushed ice (500 g). The product, 2-(*p*-methoxybenzyl)-1,4,6-trimethyl-1,2-dihydropyridine perchlorate was filtered and washed with ethanol. The dihydro perchlorate (28.0 g) was added to a mixture of 2 N NaOH (200 ml) and methanol (150 ml), and treated with sodium borohydride (7.5 g).

The mixture was refluxed for 6 - 8 hr, diluted with water (300 ml), cooled and extracted with ether (3 x 100 ml). The bulked ether extract was dried (Na_2SO_4) and the solvent was removed to give 19.20 g of 2-(p-methoxybenzyl)-1,4,6-trimethyl-1,2,3,6-tetrahydropyridine which with 150 ml of 47% aq. HBr was kept at 135 - 140°C for 22 hr. The resultant solution was poured into ice-water and made alkaline with ammonia (0.880). Extraction with chloroform (4 x 100 ml) followed by drying and evaporation gave the crude product as an oil which on washing with anhydrous ether gave the *product* as a solid (6.9 g, 33%). Recrystallisation from ethanol afforded a solid, m.p. 234 - 236°C.

Anal. calcd. for $C_{15}H_{21}NO$ requires

C, 77.88; H, 9.15; N, 6.05%:

Found: C, 78.09; H, 9.30; N, 6.00%.

The *hydrochloride* separated as colourless crystals from ethanol-ether mixture.

2'-Hydroxy-2,5-dimethyl-6,7-benzomorphan (3.45)

The titled compound was synthesised from 1,4-dimethyl-pyridinium iodide (20 g; 85 mMol) and ethereal *p*-methoxybenzyl-magnesium chloride (from *p*-methoxybenzyl chloride (39.9 g) and magnesium 18 g) following the same procedure described for 2,3,5-trimethyl-6,7-benzomorphan above. The product (9.0 g; 48%) was recrystallised from ethanol, and had a m.p. 206 - 209°C (Lit.[102] 206 - 210°C).

2'-Hydroxy-3,5-dimethyl-6,7-benzomorphan (3.*49*)

A solution of 2'-hydroxy-2,3,5-trimethyl-6,7-benzomorphan (4.10 g, 18 mMol) in acetic anhydride (10 ml) was heated together on a steam bath for 3 hr. The solvent was removed *in vacuo*, and the residue was dissolved in ethyl acetate (100 ml). After washing with 5% Na_2CO_3 solution (3 x 50 ml) the organic layer was separated, dried (anhy. K_2CO_3) and evaporated *in vacuo* to give the O-acetylated compound (4.0 g). A solution of this O-acetylated compound in chloroform (25 ml) was added dropwise to a solution of cyanogen bromide (1.60 g) in chloroform (25 ml) at room temperature. The mixture was refluxed for 3 hr, cooled to room temperature and washed with 5% HCl (50 ml). The dried (Na_2SO_4) chloroform solution was concentrated *in vacuo* to give 4.07 g of the crude *N*-cyano compound. To this crude *N*-cyano compound was added 7% HCl (80ml) and the mixture was refluxed overnight. After cooling, the solution was made alkaline with aqueous ammonia and extracted with chloroform (4 x 50 ml). The bulked chloroform extract was dried (anhy. K_2CO_3) and concentrated *in vacuo* to give the *product* as a solid (2.27 g; 59%), which was recrystallised from isopropanol and had m.p. 240 - 242°C.

Anal. calcd. for $C_{14}H_{19}NO$ requires

C, 77.38; H, 8.81; N, 6.45%

Found: C, 77.02; H, 9.13; N, 6.54%.

2-Allyl-2'-hydroxy-3,5-dimethyl-6,7-benzomorphan (3.*50*)

A mixture of 2'-hydroxy-3,5-dimethyl-6,7-benzomorphan (1.5 g; 6.9 mMol), allyl bromide (0.84 g; 6.9 mMol) and potassium

carbonate (0.5 g) in ethanol (50 ml) was refluxed for 24 hr, and the solvent was removed *in vacuo*. The residue was taken up in water and extracted with chloroform (3 x 100 ml). The bulked chloroform extract was dried (Na_2SO_4) and concentrated to give the *product* as a solid (0.84 g, 48%).

The *hydrochloride* crystallised from butanone-methanol mixture and had m.p. 263 - 265°C.

Anal. calcd. for $C_{17}H_{24}NOCl$ requires

C, 69.49; H, 8.23; N, 4.77%:

Found: C, 69.11; H, 8.23; N, 4.81%.

2-Cyclopropylmethyl-2'-hydroxyl-3,5-dimethyl-6,7-benzomorphan (3.51)

A solution of cyclopropylcarbonyl chloride (1.88 g; 18 mMol) in tetrahydrofuran was added dropwise to a mixture of 2'-hydroxyl-3,5-dimethyl-6,7-benzomorphan (2.0 g; 9.2 mMol) and triethylamine (1.81 g; 18 mMol) in tetrahydrofuran (50 ml). The mixture was stirred at room temperature for 3 hr, after which the precipitate of triethylamine hydrochloride was filtered off.

Evaporation of the tetrahydrofuran gave (3.04g; 93%) of the cyclopropylamide of (3.49). A solution of the cyclopropylamide in tetrahydrofuran (40 ml) was added dropwise to a suspension of lithium aluminium hydride (0.97 g) in anhydrous tetrahydrofuran. The mixture was refluxed for 8 hr after which the excess lithium aluminium hydride was destroyed with H_2O (0.97 ml), followed by 5 N NaOH (0.80 ml) and finally, H_2O (2.9 ml). The filtrate obtained

after removing the precipitate was dried (Na_2SO_4) and concentrated to give the *product* as an oil (1.41 g; 61%) which solidified on standing.

The *hydrochloride* separated as colourless crystals from ethanol-ether mixture and had m.p. 280 - 282°C.

Anal. calcd. for $C_{18}H_{26}NOCl$ requires

C, 69.59; H, 8.54; N, 4.55%:

Found: C,70.05; H, 8.66; N, 4.61%.

2'-Hydroxyl-2,4,5-trimethyl-6,7-benzomorphan (3.*54*)

To a cooled and stirred ethereal solution of 2-cyano-1,4,5-trimethyl-1,2,3,6-tetrahydropyridine (6g; 40 mMol) was added an ethereal solution of *p*-methoxybenzyl magnesium chloride (from *p*-methoxybenzyl chloride, 18.78 g and magnesium, 8.64 g). After 2 hr the mixture was quenched with ice (50 g), the ether layer was separated and the aqueous phase washed with ether (2 x 100 ml). The combined ether solution was extracted with aq. 2N HCl (3 x 100 ml), and the acid extracts were basified with dilute ammonia solution and extracted with ether (3 x 100 ml). Evaporation of the dried (Na_2SO_4) ethereal solution gave 2-(*p*-methoxybenzyl)-1,4,5-trimethyl-1,2,3,6-tetrahydropyridine (8.2; 83%), which was heated in boiling aq. 47% HBr (60 ml) under reflux for 22 hr. The cooled solution basified with dilute ammonia, was extracted with chloroform (4 x 100 ml), the chloroform solution was extracted with 2 N HCl (3 x 100 ml) and the combined acid extracts were basified with dilute ammonia solution. Chloroform extraction (4 x 100 ml) followed by

evaporation of the dried (Na_2SO_4) extract gave the product as a solid (2.46 g; 32%).

The *hydrochloride* separated from ethanol-ether mixture as colourless crystals and had m.p. 283 - 285°C (with decomposition).

Anal. calcd. for $C_{15}H_{22}NOCl$ requires

C, 67.27; H, 8.28; N, 5.23%:

Found: C, 66.87; H, 8.55; N, 5.23%.

2-Cyano-5,9-dimethyl-6,7-benzomorphan (5.7)

To a stirred, ice-cooled solution of CNBr (4.76 g) in dry chloroform was added a solution of 2,5,9-trimethyl-6,7-benzomorphan (7.0 g) in chloroform (100 ml) during 15 min. The mixture was stirred at room temperature for 1 hr and then heated under reflux for 2 hr. The solvent was evaporated, and the residue was treated with a mixture of water (50 ml) and ether (100 ml). The ether layer was separated and the combined ether layer and ether washings (2 x 50 ml) of the aqueous layer were washed successively with water (2 x 50 ml), 2N HCl (2 x 50 ml), 10% aq. Na_2CO_3 (2 x 50 ml) and dried (Na_2SO_4). Removal of the solvent *in vacuo* gave the 2-cyano compound as an oil (5.60 g; 76%) which solidified on standing after purification on a column of silica

ν_{max} (Nujol): 2220 cm^{-1} (-C≡N)

^{13}C n.m.r. spectrum: -C≡N 118.32 ppm

2-(N'-Phenylamidino)-5,9-dimethyl-6,7-benzomorphan (5.*8*)

This is a general procedure for other 2-arylamidino-6,7-benzomorphans.

A mixture of 2-cyano-5,9-dimethyl-6,7-benzomorphan (1 g; 4.5 mMol) and anilinium *p*-toluene sulphonate (1.26 g; 4.5 mMol) was heated under reflux in a mixture of pyridine (0.70 g) and toluene (5 ml) for 3 hr. The solvent was removed *in vacuo* and the residue was taken up in aqueous ethanol. The aqueous ethanolic solution was basified with 20% NaOH and extracted with ether (3 x 100 ml). The combined ether extract was dried (Na_2SO_4) and removal of solvent gave 1.20 g of the crude product. Extraction of this crude with petroleum spirit (60 - 80) and silica column chromatography, gave the *product* as an oil (0.90 g; 63%) which solidified on standing. The base crystallised as needles from petroleum spirit (60 - 80) and had m.p. 140 - 142°C.

Anal. calcd. for $C_{21}H_{25}N_3$ requires

C, 78.99; H, 7.83; N, 13.16%:

Found: C, 79.03; H, 8.00; N, 13.25%.

The *hydrochloride* separated as colourless crystals from ethanol-ether mixture and had m.p. 234 - 237°C.

ν_{max} (KBr): $\diagdown C=\overset{+}{N}H \diagup$ 1660 cm^{-1}

Anal. calcd. for $C_{21}H_{26}N_3Cl$ requires

C, 70.83; H, 7.30; N, 11.80:

Found: C, 70.33; H, 7.49; N, 11.78%.

2-(N'-p-tolylamidino)-5,9-dimethyl-6,7-benzomorphan (5.*9*)

By the method described for (5.*8*), p. 169, 2-cyano-5,9-dimethyl-6,7-benzomorphan (1g, 4.4 mMol) and *p*- toluidinium-*p*-toluene sulphonate (1g, 4.9 mMol) afforded the titled *product* as an oil (0.73g; 50%) which solidified on standing. The base crystallised as tiny needles from petroleum spirit (60-80°C) and had m.p. 150-151°C. Anal. calcd. for $C_{22}H_{27}N_3$ requires:

C, 79.20; H, 8.10; N, 12.61%;

Found: C, 78.15; H, 8.07; N, 12.37%

The *hydrochloride* separated from ethanol ether mixture and had m.p. 238-240°C. Anal. calcd. for $C_{22}H_{28}N_3Cl$ requires:

C, 71.45; H, 7.57; N, 11.36%;

Found: C, 70.61; H, 7.13; N, 11.26%

2-(N'-p-anisylamidino)-5,9-dimethyl-6,7-benzomorphan (5.*10*)

By the method described for (5.*8*) p. 169, 2-cyano-5,9-dimethyl-6,7-benzomorphan (1g; 4.4 mMol) and *p*-anisidinium-*p*-toluene sulphonate (14.5g, 4.9 mMol) gave the *product* as an oil (0.30g, 20%). The *hydrochloride* separated as tiny needles from ethanol-ether mixture and had m.p. 188-190°C. Anal. calcd. for $C_{22}H_{28}N_3ClO$ requires:

C, 68.48; H, 7.26; N, 10.89%;

Found: C, 65.92; H, 7.32; N, 10.46%.

Attempted Synthesis of 2-amidino-5,9-dimethyl-6,7-benzomorphan (5.*6*)

A solution of 5,9-dimethyl-6,7-norbenzomorphan (1g, 5 mMol) and 2-methyl-2-thiopseudourea sulphate (0.8g, 2.8 mMol) in 50% aqueous ethanol (50ml) was heated under reflux for 4 hr. After the removal of the solvent *in vacuo*, the oily residue was taken up in water, basified with aqueous ammonia and extracted with chloroform (3 x 50ml). Removal of the chloroform afforded an oil (0.80g).

^{1}H and ^{13}C n.m.r. spectra of the product was consistent with the structure of the starting material rather than the titled compound.

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